occupant-emitted odors. At least 15 cfm per occupant was needed to reduce the odor level to a point acceptable to 80 percent of the people entering an occupied space. This amount of ventilation was found sufficient to control tobacco-smoke odor when the smoking rate is about todays average. (PM, 3-1074)

In ASHRAE's submission to the RFI docket, Janssen writes:

> ANSI/ASHRAE Standard 62-1989 is an authoritative guide for achieving acceptable indoor air quality. The Standard defines ventilation rates needed to achieve freedom from odor, irritation and create a comfortable indoor environment. As the only nationwide consensus-based technical standard on ventilation and acceptable indoor air quality, ASHRAE recommends Standard 62-1989 as the standard of choice for adoption by reference for state and local building codes and regulations. (3-440)

A number of respondents to the RFI endorse the ventilation procedure specified in ASHRAE Standard 62-1989 and recommend its adoption as the basis to possible OSHA recommendations on IAQ. (Law Associates 3-1200; ENV Services, Inc., 3-1089; Organization Resources Counselors, Inc., 3-1084; the National Environmental Development Association's Total Indoor Environmental Quality Coalition (NEDA/TIEQ), 3-1054; Healthy Buildings International (HBI), 3-1053; Systems Applications International (SAI), 3-1052; U.S. Navy, 3-982; Stellmack Air Conditioning and Refrigeration, 3-978; Oklahoma Dept. of Labor, 3-945; Pennsylvania AFL-CIO, 3-908B; Duke Power Company, 3-860; American Association of Occupational Health Nurses (AAOHN), 3-803; American Federation of Government Employees, 3-529; ASHRAE, 3-440.)

Other respondents, including governmental and private IAQ investigators and mitigation experts, industrial hygienists and engineers, recommend use of the Standard for achieving acceptable indoor air quality. (Meckler Engineers Group, 3-1081; Theodor D. Sterling & Associates (TDSA), 3-1073; Occupational Illness Support Group Local 12, 3-1017; R.J. Reynolds Tobacco Company (RJR), 3-1087; U.S. Navy, 3-982; Business Council on Indoor Air (BCIA), 3-933; Gershon Meckler Associates, 3-879; the Center for Environmental Assessment, Inc., 3-687; Sheet Metal and Air Conditioning Contractor's National Association, Inc. (SMACNA), 3-856; International Brotherhood of Teamsters, 3-858; Consolidated Edison Company of New York, 3-828; Caterpillar, Inc., 3-805; Philip Morris Companies, 3-1074; United Technologies, 3-651; Dow Chemical Company, 3-502; Thomas E. Glavinich, D.E., P.E., 3-498; Ford Motor Company, 3-447; Systems Applications International (SAI), 3-1052.)

One of the largest private IAQ diagnostic and mitigation firms in the U.S., Healthy Buildings International, Inc., writes that "ASHRAE Standard 62-1989, 'Ventilation for Acceptable Air Quality,' is perhaps the single most useful document we have in our efforts to communicate the proper practices for ensuring good indoor air quality in commercial buildings. We support its use, continued development and incorporation into future building codes, standards and IAQ legislation." (3-1053)

The submission by Meckler Engineers Group states:

> ASHRAE Standard 62-1989 is the only recognized authority that specifies the desired performance of building ventilation systems. . . . If OSHA decides that it is appropriate to regulate workplace IAQ at the national level, adoption of ASHRAE Standard 62-1989 would be the best strategy. (3-1081)

The EPA's submission to OSHA includes its handbook for remediation of indoor air quality problems. EPA's recommendations include: "Compare design air quantities to building codes for the current occupancy or ventilation guidelines (e.g., ASHRAE 62-1989), and compare ventilation rates to ASHRAE 62-1989." The handbook also recommends that it would be "informative to see how your ventilation rate compares to ASHRAE 62-1989, because that guideline was developed with the goal of preventing IAQ problems." (EPA, 3-1075 D)

Ventilation Effectiveness: The Ventilation Rates Specified in ASHRAE 62-1989 Are Effective in the Mitigation of Poor IAQ and the Maintenance of Acceptable IAQ, According to Scientific Data and the Professional Experience of IAQ Experts

ASHRAE Standard 62-1989 prescribes the rate at which fresh or outside air must be delivered to occupied spaces and the various means to condition that air. The Standard recommends a ventilation rate of 20 cubic feet of outside air per minute per person for most commercial and non-industrial workplace facilities, with 15 cfm as the minimum ventilation rate. However, the key question is whether or not the ventilation rates specified by ASHRAE 62-1989 are sufficient to *mitigate* poor indoor air quality and to *maintain* acceptable indoor air quality. A number of submissions to the OSHA RFI provide data which support the effectiveness of ASHRAE 62-1989. For example, the submission by the National Environmental Development Associations' Total Indoor Environment Quality Coalition states that "while data do not exist to determine the optimal ventilation rate, the ASHRAE Standard [rate] of 20 cubic feet per minute per person appears to maintain adequate air quality in environments where the HVAC systems are designed to deliver that ventilation, and where those systems are properly maintained." (3-1054)

The Food and Allied Services Trade Union states that ensuring an adequate fresh air supply "has been shown to be the single most effective method of correcting and preventing problems and complaints related to poor indoor air quality. . . . fresh outdoor air should be adequately distributed to all office areas during the entire time they are occupied, at a minimum rate of 20 cfm per person." (3-434)

A number of recently published studies on ventilation effectiveness also support the ventilation rates of ASHRAE 62-1989. In 1991, Menzies et al. concluded, after examining the effect of various levels of outdoor ventilation on sick-building syndrome symptoms, that "increasing the amount of outdoor air from 20 to 50 cfm per person did not result in a reduction of symptoms considered typical of SBS among office workers."[73] The authors concluded that "this study supports the continued use of 20 cfm pp as the minimum standard for the supply of outdoor air to indoor non-industrial space." Similarly, Nagda et al. reported on a study conducted in a 20-story government office building. Although they reported limited differences in measured and perceived indoor air quality comfort complaints, they concluded that "occupants consistently reported fewer health symptoms in the presence of higher ventilation."[74] (PM, 3-1074)

IAQ investigators Downing and Bayer recommend, as part of their operation and maintenance procedure checklist for achieving acceptable indoor air quality, raising "outdoor air ventilation to ASHRAE-recommended minimums."[66] This recommendation has led to improved perception of IAQ by occupants in more than 80 percent of the investigations completed to date by the researchers. (PM, 3-1074)

In a sick-building case investigation featured in *Indoor Air Quality Update* (October 1991), investigators reported "uncomfortable environmental conditions in all locations due to inadequate air flow rates, which range from 30 percent to 70 percent below the ASHRAE design standard of 20 cfm/person in office environments."[75] The investigators recommended an increase of fresh air ventilation in accordance with the ASHRAE Standard for ventilation in order to "improve air circulation and comfort levels." (PM, 3-1074)

Hicks (1984) reported reduced symptom prevalence of eye irritation, sinus congestion and headache when outside air ventilation rates were increased in two buildings in California. In the first building, an increase in the ventilation rate from 5-7 cfm/person to 25-32 cfm/person led to a reduction in symptom prevalence from 60-73 percent to 25-32 percent. Similar results were reported in the second building, where an increase in ventilation from 4 cfm/person to 22 cfm/person lead to a reduction in symptoms (from 48-57 percent to 23-34 percent). (Reported in TDSA, 3-1073) These data support the claim that compliance with ventilation rates specified in ASHRAE Standard 62-1989 (i.e. 20 cfm/person) has a positive impact on occupant comfort perceptions.

Investigators from HBI, Inc. recently reported on an indoor air quality investigation in a school in which they recommended, in order to "prevent the build-up of all indoor airborne pollutants within the building . . . that ASHRAE's suggested ventilation rate of 15 cfm/person be obtained throughout the building during times of occupancy."[76] Similarly, Turner and co-

workers investigated 29 different schools in which they reported that the "amount of ventilation being provided was, in general, found to fall short of the current ASHRAE Standard 62-1989 guidelines." The researchers recommended that each school operate under the ventilation rates prescribed by ASHRAE Standard 62-1989.[77] (PM, 3-1074)

The effectiveness of ASHRAE Standard 62-1989 for dilution of PTS constituents has also been evaluated by scientists. In 1990, researchers presented results of their work comparing the effects of increased ventilation recommended by ASHRAE 62-1989 in areas where smoking is permitted and in areas where it is prohibited.[78] Through the aid of computer models, the researchers demonstrated that air quality in the areas where smoking is permitted does not differ significantly from the quality of air in nonsmoking areas, where both areas are supplied with outdoor air at levels recommended by ASHRAE 62-1989. (Holcomb, 3-1065)

In their review of PTS-related air quality monitoring in different workplaces under various smoking conditions, researchers from TDSA Ltd. conclude "in office areas in which (a) smoking is allowed, and (b) outside air ventilation rates meet or exceed the ASHRAE ventilation standard, nicotine concentrations have typically been less than 5 ug/m^3 and respirable suspended particle levels have ranged between 20 ug/m^3 and 60 ug/m^3.[16,22,42] (TDSA, 3-1073)

In their submission to the OSHA docket, scientists from HBI, Inc. summarized the results of a paper entitled "The Measurement of Environmental Tobacco Smoke in 585 Office Environments."[41] (HBI, 3-1053) The authors write:

> Computer analysis shows that when 'blindfolded' for presence or absence of smokers, in most cases realistic smoking levels do not significantly influence the aspects of air quality that were measured, and spill over from smoking areas into nonsmoking areas appears to minimal. This work further reinforces the position the American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) has taken on ETS in office buildings in ASHRAE Standard 62-1989 (1989), that acceptable air quality can be maintained in properly ventilated offices with a moderate amount of smoking, even without smoker segregation.

Professor Alan Hedge offers the following observation on the basis of his extensive experience in monitoring PTS constituents during investigations of sick-building syndrome: "Our data show that modern ventilation systems are capable of diluting the small pollutant loads from smoking at the levels which we observe, without necessarily exposing nonsmokers to significant elevated levels of indoor air pollutants." (3-955)

Company scientists from R.J. Reynolds reported on a recently completed study of four office buildings. (RJR, 3-1087) Two of the buildings investigated had a policy of unrestricted smoking; in the other two buildings, smoking was restricted to separately exhausted lounges. Regardless of smoking policy, RJR reports all ventilation and indoor air quality indicators were "well within applicable standards." The authors write:

> In summary this study demonstrates conclusively (a) that with an HVAC system that is adequately designed, operated in accordance with current ASHRAE standards and properly maintained, all indicators for PTS are at extremely low, *de minimis* levels, even in the presence of substantial smoking activity, and (b) that such smoking activity has a negligible effect on contaminant levels in buildings where smoking is unrestricted. (3-1087)

RJR concludes:

> RJR believes, based on its own detailed research and the consistent results of other workplace assessments, that a properly designed and maintained HVAC system that is operated in accordance with the ventilation rate procedures of the ASHRAE Standard 62-1989, will be effective in assuring that exposures to PTS will be *de minimis*.

Based on their own case studies, the National Energy Management Institute (NEMI) acknowledges that exposure "to the odor caused by excessively high concentrations of PTS can be annoying to nonsmokers." NEMI suggests that "several avenues exist to address this problem. First and foremost is to apply the ASHRAE 62-1989

ventilation standard . . . workplaces operating in accordance with ASHRAE 62-1989 will not have PTS annoyance problems because the ventilation system will effectively remove all smoke." (3-1183)

In their comprehensive review of indoor air quality in non-industrial occupational environments, Morey and Singh write that "ASHRAE Standard 62-1989 is probably the most important document in the IAQ literature."[79] (Morey, 3-505) They note:

> It reflects a consensus reached since 1983 by knowledgeable individuals from engineering, industrial and academic groups. Janssen points out that the ventilation rates recommended in Standard 62-1989 for the most part are similar to 'recommended' rates in Standard 62-1973 and to the rates recommended for smoking environments in Standard 62-1981.
>
> A key feature of Standard 62-1989 and its ventilation rate procedure is the increase in the minimum outdoor ventilation rate from 5 to 15 cfm per person. Outdoor air requirements recommended by the ventilation rate procedure make no distinction between 'smoking-allowed' and 'smoking-prohibited' areas. A minimum of 15 cfm of outdoor air per person as specified in the ventilation rate procedure is recommended because new research indicated that this is the minimum amount of outdoor air needed to dilute body and tobacco smoke odors to acceptable levels. The outdoor air requirements specified in the ventilation rate procedure must be delivered to the occupied zone. Design assumptions with regard to ventilation rates and air distribution to the occupied zone are required by Standard 62-1989.
>
> Standard 62-1989 also requires that the design documentation for a HVAC system state clearly which assumptions are used in design. This allows others to estimate the limits of the HVAC system in removing air contaminants prior to commissioning and prior to the introduction of new contaminant sources into the occupied space.
>
> A key provision in Standard 62-1989 now requires that when the supply of air to the occupied zone is reduced (for example, in VAV systems), provision be made to maintain minimum flow rates of outdoor air throughout the occupied zone.

The Building Systems Approach is Cost-Effective; Costs Due to Increased HVAC Use Are Likely to be Minimal and Offset by Improvements in Worker Comfort and Well-Being

Critics of the building systems approach to acceptable indoor air quality suggest that initial construction costs, operating costs and maintenance costs associated with increased ventilation would be burdensome to the building owner or manager. However, this claim does not appear to be supported by any specific data submitted in response to the OSHA RFI. On the contrary, published data indicate that initial and operating costs associated with increased ventilation rates specified in ASHRAE 62-1989 would be minimal, and that maintenance costs would be virtually unaffected by an increase in ventilation. Indeed, the data suggest that any increased costs associated with the building systems approach would be more than offset by a reduction in employee absenteeism and complaints, and a potential improvement in worker productivity. Many respondents to the OSHA RFI believe that the building systems approach may be the most cost-effective approach to the maintenance of acceptable indoor air quality. (For a review of the RFI Docket on the costs of upgrading ventilation systems, see Appendix V.)

Data submitted to the OSHA RFI specifically address the anticipated and real costs associated with the adoption of the ASHRAE Standard 62-1989 "Ventilation for Acceptable Indoor Air Quality." The Standard has already been adopted in 12 states and by 2 major building code organizations in the United States. It is currently under consideration for adoption by the remaining national building code organizations. If adopted by building code organizations, municipal and local governments in the U.S. will include the Standard as part of their local governing building code. ASHRAE 62-1989 will then serve as the design standard for ventilation for all *new* and *retrofitted* buildings.

An earlier version of the ventilation standard, ASHRAE 62-1973, specified a recommended ventilation rate of 15 cfm/person. The 1973 version of the Standard was incorporated into building codes and was in effect throughout the 1980s. (ASHRAE Standard 62-1981, which specified a minimum ventilation rate of 5 cfm/person, did not receive approval by ANSI and was not adopted by building code organizations.) There are few differences in design specifications between the recommended ventilation rates in Standard 62-1973 and the minimum ventilation rates specified in ASHRAE Standard 62-1989. Therefore, capital (initial or first) costs are not likely to be appreciably higher for the 1989 version of the Standard than those required by ASHRAE 62-1973.

It is recognized by contributors to the OSHA RFI that any increased costs associated with the adoption of ASHRAE 62-1989 will vary according to specific workplace configurations. Both the 1973 and 1981 versions of Standard 62 permitted a minimum ventilation rate of 5 cfm/person, compared with the minimum rate of 15-20 cfm/person specified by ASHRAE 62-1989. Energy costs associated with the operation of ventilation systems in compliance with the minimum recommendations in ASHRAE 62-1989 therefore can be expected to increase annual energy budgets for some buildings, depending upon the location of the building.[80-84] However, maintenance costs for HVAC systems should not vary appreciably from those in compliance with either the 1973 or 1981 versions of the ASHRAE Standard.

The impact of increased (outside air) ventilation rates upon initial costs and annual operating costs has been assessed by researchers from Lawrence Berkley Laboratory (LBL).[80-81] Using a series of computer simulations, the authors estimated changes in initial and operating costs associated with increasing minimum outside air supplies from 5 cfm/person to 20 cfm/person. The prototype for the simulations was a standard 100,000 ft^2 building in 13 different locations throughout the United States and Canada. Estimated capital costs for HVAC equipment were small, amounting to less than 5 percent of total building costs or, at most, 35 cents/ft^2. Operating costs for heating were estimated to increase by a maximum of 8 percent annually; costs for cooling increased to a maximum of 14 percent. Average annual energy operating costs were estimated to increase by about 3-5 percent overall. (TDSA, 3-1073)

In 1990, the LBL authors extended the computer simulations to apply to small and medium size office buildings.[82] Annual energy costs were estimated to increase about 5 percent for small office buildings and 3 percent for medium sized offices. (TDSA, 3-1073)

Recent testimony from The Sheet Metal and Air-Conditioning Contractors National Association (SMACNA) before Congress describes another simulated study which estimates that an increase from 5 to 20 percent outside air would cost an additional $1,800 in annual energy expenditures for a 100,000 square foot office building.[83] This is equivalent to an increased operating cost of about $0.02 per square foot. (SMACNA, 3-1073)

The submission from the BCIA reports:

> The Bonneville Power Authority and the Department of Energy have both estimated that the energy penalty for bringing ventilation rates into compliance with the ASHRAE Standard would be in the range of 4 to 5 percent regardless of the buildings type or location . . . an analysis by Flatheim concluded that increased energy consumption resulting from upgrading IAQ may total as much as 8 percent, but is more than compensated for by a 1 percent improvement in productivity. (3-933)

The BCIA submission continues:

> The costs of complying with the ASHRAE Standard will depend, in large part, on the building size and location. For a 36,000 square feet building in southern California the costs associated with increasing the ventilation from 5-20 cfm/person was $0.25 to $0.30 per square foot per year. This cost was associated with cooling and did not involve additional ducting-zoning costs or any control costs.

The submission from TDSA Ltd. reports on an estimate of the incremental capital costs of incorporating the ASHRAE Standard into a 200,000 ft^2 office building. The researchers note that the mechanical engineers' initial estimate of the increased capital costs was less than $7,000, or approximately $0.04/$ft^2$, for a building project budgeted at $20,000,000. (TDSA, 3-1073)

Comments from Mr. Joseph Ventresca report on a model energy consumption simulation for a 100,000 ft² office building located in Columbus, Ohio.[84] Cost increases associated with an increase in outside air from 5 to 20 cfm/person were: "Heating energy increases of 0 percent to 8 percent; cooling energy increases of 1 percent to 14 percent, electric demand increases of 0.5 percent to 8 percent; insignificant fan energy increases; and total energy cost increases of less than 5 percent." (Ventresca, 3-941)

Additional submissions to the OSHA RFI docket suggest that increases in ventilation rates to meet ASHRAE Standard 62-1989 will not necessarily increase annual energy budgets. (EPA, 3-1075D; G. Meckler, 3-879; Ventresca, 3-941) TDSA Ltd. concludes that any "increased costs are minimal, both in real terms and in relation to the potential savings in reduced absenteeism and improved productivity associated with increased occupant satisfaction with indoor environmental condition." (3-1073)

Other submissions to the OSHA RFI docket agree with TDSA Ltd.'s analysis. For example, in SMACNA's building energy cost simulation study, additional outside air ventilation was estimated to increase energy costs by about $1,800 on an annual basis for a 100,000 square foot building.[83] According to SMACNA, the same study "compared the cost of absent or sick workers affected by unhealthy ventilation and concluded that increased ventilation costs 1/135 of the costs of absent and sick employees." (SMACNA, 3-856)

In a 1991 publication, Mr. Peter Binnie describes a hypothetical situation where energy costs for maintaining acceptable IAQ are considered in terms of employee absentee rates.[85] He writes:

> Consider the following situation. In a typical building of 100,000 square feet, the move from 20 cubic feet per minute (10 litres per second) of fresh air per person down to, say, 5 cubic feet per minute (2.5 litres per second) per person may on average result in cost savings of perhaps $20,000 per annum. This could represent a 40% savings in the energy costs associated with ventilation, or 10-15% of the building's overall energy budget. Everyone in upper management would be pleased, and one can be certain that future years' budgets would be reduced to reflect the actual costs of this first year. Thus, the building is now doomed to function with no more than 5 cubic feet per minute (2.5 litres per second) per person. As HBI, ASHRAE and many others have found, this action results in unacceptable indoor pollution and increased absentee rates.
>
> In the United States and Europe, offices are commonly staffed with a generous average of 150 square feet of space per employee. Thus, in the hypothetical building of 100,000 square feet, there would be 67 staff. If they are paid the minimum wage of $15,000 per annum, the payroll bill would reach $10 million per annum. This means that every 1% of absenteeism would cost $100,000 per annum. Surely a decision to save $20,000 per year on energy that results in reducing worker productivity and increasing absentee rates involving hundreds of thousands of dollars in costs is poor business judgment. (Armitage, 3-934)

Similarly, a 1990 report issued by the United States Air Force estimates the following:[86]

> The cost of personnel in the Air Force averages about $250.00 per square foot per year. The maintenance and energy costs for all operations in a building rarely exceed $7.00 per square foot per year. Of the $7.00, no more than $2.00 are energy costs. If the unlikely proved true and we saved half of all energy costs by running closed or minimum fresh air cycles, that would be $1.00/sq ft/yr. This is the equivalent of seven hours per square foot of personnel time. This is less than two minutes per day per year. If only two minutes per day productive time is lost, then all energy savings are wiped out. Respiratory disease is at least 1.5 to 3 times more likely in a tight environment. Common respiratory infection episodes last eight to ten days with one to two days of absence being usual. The average number of respiratory infections involving colds and flu is one per person per year based on National Center for Health

Statistics data. Tight buildings are likely to raise that number to between 1.5 and 3.0 episodes per person per year. Using the lower figure of one day of loss per episode, we have raised the lost days from one to between 1.5 and 3 per person per year with an average of 2.25 days. This is an average increase of 1.25 days. By this measure alone we have lost 10 hours, three more than is required to put us in the deficit column. Three of the days of infection are likely to suffer from reduced productivity by at least 20% for a total of 60% of a day. Cost is now 1.85 excess days lost; 1.85/220 = 0.84% x $250/sq ft/yr = $2.10/sq ft/yr. This cost already exceeds the savings possible by running the air handler with inadequate fresh air by 2.1 times. This analysis does not begin to address the losses due to aggravation of pre-existing problems such as asthma and allergies, the cost of other diseases known to result from improper maintenance and operation of air handlers, the loss in productivity due to irritant effects of poorly controlled 'comfort' parameters or the losses due to the social atmosphere surrounding the problems generated. The actual savings from running closed cycle are even less than the generous $1.00 we allowed. It is usually necessary to increase total outside added air from roughly 10% of total flow to obtain adequate fresh air and control CO_2 to appropriate levels. If all of the $2.00 were going to climate control, this represents only 20 cents rather than a dollar in savings. Since this is so, the actual relative loss from increase in infections is $2.10/0.20 = 10.5 times the possible energy savings if all energy is used for heating. This is a poor bargain. (PM, 3-1074; Poitrast, 3-34)

Several researchers have argued that the costs of increased worker absenteeism attributable to poor indoor air quality would greatly exceed any energy expenditures due to increased ventilation. Using a 100,000 square feet office building as an example, researchers have estimated that increased energy costs for a year would be equivalent to costs associated with _ day of absenteeism over the buildings entire workforce.[85] (HBI, 3-1053; Armitage, 3-934) Another investigator suggested that a one percent absenteeism rate would be equivalent to an expenditure of over $100,000 annually, compared to an increased annual cost for ventilation of $20,000.[87]

Thus any anticipated cost increases due to incorporation of ASHRAE 62-1989 will be offset by improvements in productivity and projected reductions in absenteeism. One reviewer notes:[87]

> The enlightened owner or energy manager must develop a new perspective of energy costs and comparable air quality costs. It has been suggested that such a comparison could compare the annual cost of energy on a square foot basis to the annual cost of human capital on a square foot basis. The latter 'productivity factor' would use annual wage and salary and health cost line items and divide by the occupied office space. Using a typical comparison, energy could be assumed at around $3.00 sq/ft/yr, but human capital will typically be as much as $300 sq/ft/yr. From this perspective, even a dramatic change of 25-50 percent of energy costs equates to only a few minutes of human capital time . . . or productivity. Productivity therefore becomes the dramatic dominant economic factor. (3-1074)

Source Control: The Alternative Mitigation Strategy for Poor IAQ

Scientific data support the effectiveness of the ventilation rates prescribed by ASHRAE Standard 62-1989 for improvement and maintenance of indoor air quality. The ventilation rates were specifically designed to "control carbon dioxide and other contaminants with an adequate margin of safety, to account for variations among people, varied activity levels, and a moderate amount of smoking."[69] The available published scientific literature submitted to the OSHA RFI docket supports this position.

Several submissions to the OSHA RFI docket reject the building systems approach and recommend that more attention be given to controlling sources of indoor air pollution. Advocates of source control argue that (1) the costs associated with increased ventilation will be prohibitive; (2) a building systems approach would generate unnecessary regulations and government involvement in business, and (3) particular chemical agents can be identified at exposure levels that constitute risks to workers, and the agents' removal will not incur significant cost.

Source Control: Fails to Address Total IAQ and is Not Supported by Data on Source Strengths, Exposures or Health Effects

The building systems approach and the source control approach to IAQ are not necessarily mutually exclusive, but a large part of the source control strategy would appear to be the result of a misunderstanding of the IAQ issue. This fundamental misunderstanding generates mitigation strategies which fall short of satisfying objectives for total acceptable indoor air quality. For example, a source control strategy cannot address the fundamental issues of the building systems approach, namely, the dilution and removal of by-products of human metabolism and non-industrial work-related activities. The ventilation rates prescribed by ASHRAE 62-1989 are intended to effectively dilute and remove water vapor, carbon dioxide, odors and particles associated with human metabolism, as well as the by-products of work-related processes and activities typically found in an office, school or retail setting. Such processes or activities range from simple movement (and the raising of dust particles from carpets) to food preparation, cleaning, copying and smoking.

Sole reliance upon source control for achieving acceptable indoor air quality ignores another fundamental principle of the building systems approach, i.e., that a specific airborne source often cannot be identified and associated with complaints about IAQ. Even advocates of source control recognize this failure. For example, one proponent writes that while the importance of a source is "a function of the health effects of its emissions . . . not enough is known about these effects." Moreover, the author realizes that "we are unlikely to have a great deal more information about health effects in the foreseeable future." Indeed, it is also recognized that "even the strength of source emissions is not well understood for most products."

The advocate of source control fails to acknowledge that the presence of *some* constituents in indoor air is unavoidable, and that inadequate ventilation has been identified as one of the major causes of complaints about IAQ. Source control addresses neither of those issues.

Other potential problems associated with a source control approach to IAQ could be insurmountable. For example, of the thousands of possible constituents in indoor air, which are to be "controlled at the source?" Who will decide — a building manager, operator, or an indoor air quality mitigation expert? Will indoor air quality monitoring be required for all non-industrial workplaces? (This would constitute a cost-prohibitive recommendation; see Appendix VI concerning the costs of monitoring and laboratory analysis for indoor air pollutants.) At what level of exposure would a program for removal of a given source be activated? The latter question presupposes the development of a program of PELs or TLVs for exposures to potential

substances in the non-industrial workplace, which would be presumably different than those specified by OSHA for industrial workers. Yet, by the admission of the advocates of source control, such a program could not be based on actual data because source emissions are "not well understood for most products." (Levin, 1991)

A Source Control Example: The Smoking Ban

A smoking ban is the most common example of the source control strategy, perhaps because it is perceived as a quick, simple and inexpensive "solution" to complaints about IAQ. Advocates of the smoking ban argue that only a ban will eliminate the purported "risk" associated with exposure to ETS in the workplace. (ASH, 3-991 and 3-1030; Repace and Lowrey, 3-1061; EPA, 3-1075)

The 1986 Surgeon General's Report suggested that simple separation of smokers and nonsmokers would not eliminate exposure to ETS, and this position is relied upon by advocates of the smoking ban. However, the Surgeon General's opinion was not based upon actual scientific data regarding the efficacy of simple separation of smokers and nonsmokers. Moreover, the implementation of a smoking ban as a approach to the mitigation of IAQ problems ultimately fails to address critical IAQ issues. For example, the smoking ban advocate completely ignores compelling data from the various sick-building syndrome databases which indicate that rarely, if ever, are complaints about indoor air quality related to smoking. The smoking ban proponent also ignores additional data that suggest that typical nonsmoker exposure in the workplace is minimal, that epidemiologic studies on reported exposures to PTS in the workplace and chronic disease do not support the claim that PTS poses an increased risk for nonsmokers, and that the ventilation rates prescribed by ASHRAE 62-1989 will effectively dilute and remove PTS constituents from the workplace. A smoking ban itself will do nothing to improve fresh air ventilation, and nothing to address exposure to other substances in the indoor air.

A number of submissions to the OSHA RFI docket confirm the foregoing criticisms of the smoking ban. For example, according to the American Federation of Government Employees:

> AFGE's experience indicates while PTS may be a problem in a small number of situations, complaints of smoke in the air are generally a symptom of a poorly designed and maintained ventilation system. Nevertheless, some employers seek to ban or restrict smoking to eliminate the visible symptoms of ventilation, and thus divert attention from a host of unseen toxic substances commonly found in the work environment. (3-529)

Similarly, another union observes:

> Poor air quality is often blamed on smoke. While second hand smoke may contribute to a problem, it is poor ventilation that is a real cause of the problem. Workers are divided emotionally, smokers vs. nonsmokers, and a solution to poor indoor air quality is negotiated on the smoking issue alone. Then, improving the ventilation system is postponed until the smoking policy is given ample time to fail. (SEIU 3-630)

Building investigators from HBI have noted:

> Smoke accumulation within offices may be only the tip of the iceberg. If smoke is trapped by bad ventilation so are all other indoor pollutants. Many of these invisible chemicals, dust, fibers, bacteria, and fungi can have acute or long term health effects on the building occupants . . . [R]eacting solely to the visible evidence of poor ventilation omits invisible pollutants and certainly does not address the fundamental problem of inadequate ventilation. (HBI, 3-1053)

The HBI submission further suggests that "the need to implement a smoking policy in an office building often results from poor HVAC operation and maintenance practices that cause a plethora of IAQ problems, the only visible symptom of which is an accumulation of tobacco smoke." (3-1053)

The RFI submission from the Ford Motor Company undermines the fundamental assumption of the smoking ban advocates' position, i.e.:

> PTS/ETS and IAQ issues are not associated with significant air contaminant concentrations. In resolving this issue, government and management come head on into a basic philosophical dilemma of should there be one set of air contaminant limits for the office and one for the shop floor. If one subscribes to the theory that PTS/ETS in the concentrations normally found in offices is carcinogenic, then one would also have to conclude that most workers in factories and garages are exposed to harmful levels of carcinogens. Even conservative epidemiological studies suggest that this type of epidemic does not exist in the American workplace. (3-447, 3-433)

Thus, a smoking ban is a one-dimensional approach to indoor air quality — one which does not improve fresh air ventilation and one which will not ensure acceptable indoor air quality. This clearly has been recognized by ASHRAE in its recent revision of its Standard for Ventilation, Standard 62-1989. ASHRAE rejected ventilation rates which were predicated solely on the presence or absence of smoking. (Standard 62-1981)

Even the staunchest proponents of source control appear to concede that smoking bans will not improve ventilation or address other substances in indoor air. An EPA health official was quoted as saying recently "looking for single chemical contaminants isn't the answer" to the problem of indoor air quality.[88] In that same article, the director of the EPA's Indoor Air Division, Robert Axelrad, stressed that "people should not be allowed to believe that addressing smoking will solve (all indoor air quality problems)" in spite of his belief that tobacco smoke is "the most prevalent pollutant." Said Axelrad: "There are hundreds of other contaminants that need to be addressed." (PM, 1074)

A smoking ban, therefore, represents a "solution" which may not appreciably reduce nonsmoker exposure to substances in the indoor air, because it fails to address the issue of *total* indoor air quality.

Other Workplace Smoking Policy Options

While a smoking ban represents an extreme and apparently misguided approach to total indoor air quality, some individuals report annoyance and even irritation by the sight or smell of tobacco smoke. Such complaints about exposure to PTS typically have been addressed by employers with one or more of the following:

1. Increase outdoor air ventilation to levels specified in local building codes, or more recently, to levels specified in ASHRAE Standard 62-1989 "Ventilation for Acceptable Indoor Air Quality;"
2. relocation of a work station;
3. grouping of smokers and nonsmokers;
4. the use of partitions in "open" office settings; and
5. the use of desk top air cleaners or "smokeless ashtrays" for smokers.

Such measures have been effective historically in addressing complaints about PTS and require few additional costs from an employer. These remedies are based on the concept of accommodation for both smokers and nonsmokers. In addition, and more important, scientific data submitted to the OSHA RFI docket indicate that these common solutions, including adequate ventilation and the simple separation of smokers and nonsmokers, are effective in providing acceptable indoor air quality and for minimizing nonsmoker exposure to ETS.

Simple Separation of Smokers and Nonsmokers, Even Under Conditions of Recirculation, Effectively Minimizes PTS Exposure of Nonsmokers: Data Do Not Support a Significant Reduction in PTS Exposures (or "Risk" Imputed to PTS Exposures) Beyond Adequate Ventilation and/or Simple Separation of Smokers and Nonsmokers

A number of studies in the published literature have evaluated exposure to PTS constituents under various kinds of smoking policies. Typical constituents measured include: respirable suspended particulates (RSP), UV-PM, nicotine, carbon monoxide and carbon dioxide. The measurements are undertaken in both smoking and nonsmoking areas, usually under general recirculation conditions.

The results reported in the published literature indicate that simple separation of smokers and nonsmokers, under general recirculating ventilation

conditions, can reduce nonsmoker exposure by as much as 80-98%.

One recent study reported that the use of designated smoking areas reduced exposure to PTS by as much as 95%.89 Another study of a smoking-restricted office building reported that ambient nicotine in nonsmoking areas was virtually undetectable, suggesting that PTS had a negligible impact on the nonsmoking areas of the building.[90] (PM, 3-1074)

Canadian researchers, in a series of reports, presented results on levels of PTS constituents in offices where smoking was regulated and unregulated. They reported no significant differences in average PTS constituent levels between nonsmoking offices that received recirculated air from designated smoking areas and nonsmoking offices that did not receive recirculated air.[16,22,42] Nicotine concentrations reported for nonsmoking areas were marginally about limits of detection; there were no measurable differences in RSP or CO levels in nonsmoking areas that did or did not receive recirculated air from smoking areas. (TDSA, 3-1073) They concluded:

> The results indicate that the provision of a designated, but not separately ventilated smoking area can effectively eliminate or drastically reduce most components of environmental tobacco smoke from nonsmoking offices.

Hedge et al., in 1991 reported results of PTS constituent measurements under five different kinds of smoking policies.[91] Their results are reported below:

> A study of the effects of smoking policy on indoor air quality and sick building syndrome symptoms among 3,155 workers in 18 private sector air-conditioned office buildings is described. Five smoking policies were investigated: smoking prohibited, smoking restricted to rooms with local filtration, smoking restricted to rooms with no local air treatment, smoking restricted to rooms with separate ventilation, and smoking restricted to the open-plan cubicle workstations and enclosed offices. Levels of carbon monoxide, carbon dioxide, respirable particulates, formaldehyde, ultraviolet particulate mass, nicotine, air temperature, and relative humidity were measured at eight sample sites in each building. Approximately 30 workers at each of the eight sample sites completed an extensive questionnaire on environmental conditions, sick building syndrome symptoms, job satisfaction, job stress, smoking history, and personal details. Indoor air quality measures met the current ASHRAE 62-1989 standard. Comparison of all open-office sites between policies showed no significant differences in levels of carbon monoxide, carbon dioxide, formaldehyde or respirable particulates. Levels of ultraviolet particulate mass and relative humidity were significantly lower in buildings where smoking is prohibited, and air temperature was significantly higher in these buildings, although on average this was <1_C. Among all buildings, air temperature was the only physical measure that was significantly correlated with SBS symptoms. Smoking policy had no significant effect on sick building syndrome symptoms.

And:

> Smoking policy had a relatively small effect on IAQ for the pollutants measured. For most of these pollutants, there were no significant differences in concentration among offices in SP buildings, nonsmoking office areas in RF, RSV, and RNT buildings, and office areas in RWS buildings. There was a significant effect of smoking policy on UVPM and formaldehyde in these office areas, which was due primarily to higher levels in the RF and RSV policies. However, all concentrations of UVPM and formaldehyde were low. UVPM was not significantly correlated with gravimetric RSP, even though the UVPM samples were derived from these RSP samples. UVPM did correlate significantly with metered RSP ($r = 0.69$, $p = 0.0001$) and with nicotine ($r = 0.45$, $p = 0.002$), which suggests that UVPM is measuring particulates from ETS. (Hedge, 3-955)

Lee and co-workers (1985) evaluated the effects of a smoking policy on airborne PTS constituent levels.[92] They reported:

> A new smoking policy was implemented on a trial basis on one floor of a large modern Canadian office building. Smoking was

limited to a single enclosed room which shared the same recirculating-type ventilation system with the rest of the floor. Environmental monitoring was conducted on the test floor and a control floor during three consecutive working days both before and after policy implementation. Hourly levels of respirable suspended particulate (RSP), carbon monoxide (CO) and carbon dioxide (CO_2) were monitored on the floors and in the designated smoking area throughout the workday. Temperature and relative humidity were monitored at specific sites on each floor and the quantity of outdoor air supplied to each floor was measured on a daily basis. A voluntary questionnaire was circulated to all staff to detect any changes in personal smoking habits over the course of the study.

Results of the investigation showed statistically significant reductions of RSP and CO concentrations on the test floor. After standardization to the control floor, the test floor results indicated a reduction of RSP and CO, 23% and 7.2%, respectively. (TDSA, 3-1073; PM, 3-1074)

In 1989, Proctor and co-workers examined nicotine, respirable particulates, carbon monoxide, carbon dioxide, and volatile organics in the air of smokers' and nonsmokers' offices.[28] The data suggest very little nonsmoker exposure to various PTS constituents. The median UV-PM (ultraviolet particulate matter) level in nonsmokers' offices was 8.8 ug/m^3; the median nicotine value was 0.6 ug/m^3. Carbon monoxide and carbon dioxide levels did not differ appreciably between smokers' and nonsmokers' offices. Overall, levels of volatile organics did not differ significantly between smokers' and nonsmokers' offices. (PM, 3-1074)

Bayer and Black (1987) reached a similar conclusion in their investigation of VOC levels in smokers' and nonsmokers' offices.[49] They noted that although differences in nicotine concentrations were measured for offices of smokers and nonsmokers, no significant differences in VOC levels were discerned in smokers' vs. nonsmokers' offices. The researchers observed that "it was not possible" to correlate VOC concentrations with PTS or to attribute the source of various VOCs to PTS. (PM, 3-1074)

Recent studies on PTS constituent levels aboard commercial aircraft, including a 1989 study performed for the U.S. Department of Transportation, indicate the effectiveness of simple separation of smokers and nonsmokers in the minimization of PTS exposures.[93,94,95] (PM, 3-1074)

Similarly, Proctor (1987) monitored PTS constituents before and after a smoking ban on public transportation in the United Kingdom.[96] While nicotine concentrations decreased from 7 ug/m^3 (micrograms per cubic meter) to 3 ug/m^3 in nonsmoking compartments after the ban, particulate and CO levels remained unchanged. This suggests that PTS contributions to levels of particulates and CO in public transportation are not significant. (PM, 3-1074)

Investigators from Healthy Buildings International recently summarized results of a paper entitled "The Measurement of Environmental Tobacco Smoke in 585 Office Environments."[41] Using nicotine and particulates as markers for the presence of PTS, the investigators developed a computer model to predict whether a given set of constituent data came from a smoking or nonsmoking area. Using the constituent measurements from a given area, the computer model identified with 96 percent accuracy whether or not the area was "nonsmoking." This is, "spillover" of tobacco smoke was reported in only 4 percent of the areas. As the authors concluded:

> This finding shows that, in general, conventional office ventilation and partitioning is successful in separating smokers from nonsmokers.

And:

> Discriminant analysis shows that when 'blindfolded' for presence or absence of smokers, in most cases realistic smoking levels do not significantly influence the aspects of air quality that were measured, and spillover from smoking areas into nonsmoking areas appears to be minimal. This work further reinforces the position the American Society of health Refrigerating and Air Conditioning Engineers (ASHRAE) has taken on ETS in office buildings in ASHRAE Standard 62-89 (1989), in that acceptable air quality can be maintained in properly ventilated offices with

a moderate amount of smoking, even without smoker segregation. (HBI, 3-1053)

The studies reviewed above contain data regarding the low levels of PTS constituents purportedly "transferred" from smoking to nonsmoking areas, even under conditions involving a shared ventilation (recirculation) system. Data reported in those studies indicate that PTS constituents, and particularly nicotine, RSPs, and CO in nonsmoking areas in buildings where smoking is permitted, are often only slightly above the limits of detection, and often indistinguishable from "background" levels of such constituents which can be found in buildings in which smoking is altogether prohibited. The data support the contention that simple separation of smokers and nonsmokers effectively reduces PTS exposure in nonsmoking areas even under conditions of recirculation.

Dedicated Smoking Lounges and Other Options

Research thus indicates that compliance with ventilation rates comparable to those prescribed by ASHRAE 62-1981 and/or simple separation of smokers and nonsmokers in the workplace will effectively minimize exposure of nonsmokers to PTS constituents. Nevertheless, some employers have deemed it necessary to physically separate smokers and nonsmokers, typically by establishing a room or lounge dedicated to smoking. The cluster of smokers in a confined space, however, may place excessive demands upon an existent ventilation system. Thus, separate smoking rooms are often equipped with independent ventilation and/or exhaust systems.

ASHRAE suggests a ventilation rate of 60 cfm/person for areas dedicated as smoking lounges. In order to preclude the "migration" of tobacco smoke from the lounge into the central ventilation system, the lounge may be fitted with a exhaust to the exterior. Equipping a room with a separate ventilation and exhaust system, however, can be very costly to property owners and building managers. Indeed, a provision of a separate ventilation/exhaust for dedicated smoking areas may not be feasible because of such cost constraints, particularly for smaller businesses.

Existing technology permits partial recovery or at least minimization of increased costs due to retrofit and operation expenditures for separate smoking lounges. One such technological advance utilizes the Energy Recovery Unit (ERU), the principal for which involves the passing of air exhausted from the smoking lounge across a heat recovery wheel which then transfers the heat from the lounge to the wheel. The wheel then rotates from the exhaust air stream to the incoming supply air stream. On cold days, for example, the incoming air is heated and on warm days it is cooled. Energy recovery efficiencies have been estimated between 70 to 80 percent for such units, thereby substantially reducing operating costs incurred by increasing ventilation for a designated smoking area.

Another technological advance, discussed in OSHA RFI 3-879, involves the use of the "cold air distribution system." Such systems also make use of an "enthalpy" or heat-transference wheel used in the ERU. When properly designed, installed, and operated, the cold air distribution system permits delivery of fresh air at ASHRAE specified rates and energy costs which are far below those of traditional HVAC systems.

Another option for the ventilation system of a dedicated smoking lounge involves displacement or "plug flow" ventilation, in which ventilation (supply) air flows through the floor and moves vertically through the room and is exhausted at the ceiling. Substances present in the indoor environment such as dust, tobacco smoke, odors, bacteria, etc., will rise vertically above the room and will be removed by the exhaust. (PM, 3-1074)

All of the options listed above would require additional expenditures for retrofit, as well as increased operation costs. The options are available for those who desire to physically segregate smokers and nonsmokers in the workplace. However, no data exist, to our knowledge, which suggest that the dedicated smoking lounge will significantly reduce exposure to PTS-related constituents beyond reductions achieved by appropriate ventilation and the simple separation of smokers from nonsmokers. Indeed, data from numerous studies submitted to the RFI docket and discussed in this brief indicate that the PTS constituent burden in areas that are adequately ventilated and/or simply

segregated from smoking is minimal, with constituent levels barely above detection limits for sensitive monitors, and often otherwise indistinguishable from the air in completely "smoke-free" buildings. Thus, the submission from R.J. Reynolds observes:

> Any assessment of the need for measures to supplement a generic standard with special provisions such as mandated smoking lounges with separate exhaust or a smoking ban to reduce further any residual levels of PTS would plainly reveal that such measures would only result in an insubstantial reduction of an already *de minimis* exposure level. Accordingly, the imposition of such measures as mandated smoking lounges or smoking bans would be impermissible under this Supreme Court's direction that OSHA is authorized only to eliminate significant risks and may not seek the 'regulation of insignificant risks.' (3-1086)

Smoking Policies Conclusion

A requirement that all buildings which permit smoking must have designated smoking areas with separate ventilation and exhaust would be a costly requirement and clearly superfluous, given the scientific data regarding the simple separation of smokers and nonsmokers. Moreover, retrofit costs required for a designated area with separate air intake and exhaust could be economically burdensome to an employer or building owner.

Workplace environments are infinitely varied and smoking policies therefore need to be designed to fit the requirements of individual workplaces. The question of "feasibility" ought to be determined on an individual, case-by-case basis. In certain workplaces, it may be unnecessary to institute any change in current employer smoking policies. In others, minimal changes may sensibly accommodate the interests of the employer and smokers and nonsmokers alike.

SUMMARY

Substantive comments submitted in response to the OSHA RFI support the building systems approach to indoor air quality. The approach is supported in both theory and practice, and it has been used successfully for the mitigation of indoor air quality problems.

The building systems approach offers a *comprehensive* solution to poor indoor air quality. Attention to adequate supply air and its distribution to occupied spaces, together with proper maintenance of the HVAC system, provides a means for decreasing exposure to a wide range of substances in indoor air — a solution which remains constant over time.

The approach is *feasible* because it relies upon already existent technology and currently adopted consensus standards for ventilation. It is also *cost-effective* because an increase in outdoor air ventilation, for example, does not necessarily adversely affect annual energy budgets, and it may lead to a reduction in complaints and/or increased worker productivity.

We therefore urge OSHA to carefully consider the merits of the building systems approach during its review process.

REFERENCES

(1) Melius, J., et al., "Indoor Air Quality — the NIOSH Experience," *Ann Am Conf Gov Ind Hyg* 10: 3-7, 1984.

(2) U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Standards Development and Technology Transfer, "The NIOSH Approach to Conducting Indoor Air Quality Investigations in Office Buildings," *Indoor Air Quality Selected References*, September, 1989.

(3) Kirkbride, J., *Sick Building Syndrome: Causes and Effects*, Health and Welfare Canada, Ottawa, Canada, October 24, 1985.

(4) Kirkbride, J., et al., "Health and Welfare Canada's Experience in Indoor Air Quality Investigation," *Indoor Air '90: Proceedings of the Fifth International Conference on Indoor Air Quality and Climate*, Toronto, Canada, Volume 5, 99-106, July 29-August 3, 1990.

(5) Nathanson, T. "Building Investigations: An Assessment Strategy," *Indoor Air 90*, (Vol 1), Walkinshaw DS (ed), Fifth International Conference on Indoor Air Quality and Climate, Toronto, 107-112, 1990.

(6) Collett, C. et al., "A Database of Problem Buildings: Learning by Past Mistakes," *Present and Future of Indoor Air Quality*, C. Bieva, et al. (eds.), Amsterdam, Elsevier Science Publishers, 413-419, 1989.

(7) Woods, J., "Cost Avoidance and Productivity in Owning and Operating Buildings," *Occupational Medicine* 4: 753-771, 1989.

(8) Kim, I., "Sick Building Syndrome: M.E.'s Seek a Cure," *Mech Engineering* 112: 53-54, November, 1990.

(9) Freund, A., et al., "Success of Indoor Air Pollution Intervention Strategies," *Indoor Air 90*, Walkinshaw DS (ed), Fifth International Conference on Indoor Air Quality and Climate, Toronto, 1990: 587-591.

(10) Haghighat, F., et al., "Relationship Between Occupant Discomfort as Perceived and as Measured Objectively," *Indoor Environ* 1: 112-118, 1992.

(11) Pimm, P., et al., "Physiological Effects of Acute Passive Exposure to Cigarette Smoke," *Arch Environ Health* 33(4): 201-213, 1978.

(12) Winneke, G., et al., "Psychophysiological Response to Environmental Tobacco Smoke in an Experimental Social Setting," *Indoor Air Quality*, H. Kasuga (ed.), Berlin, Heidelberg, Springer-Verlag, 173-183, 1990.

(13) Sterling, T. and Kleven, S., "The Epidemiology of 'Sick Public Buildings'," *Indoor Air Quality: Symposium*, Buenos Aires, National Academy of Sciences of Buenos Aires, 79-96, 1989.

(14) Guerin, M., *The Chemistry of Environmental Tobacco Smoke: Composition and Measurement*, CIAR Monograph Series (ed), Max Eisenberg, (Lewis Publishers: Chelsea, Michigan, 1992).

(15) Kirk, P., et al., "Environmental Tobacco Smoke in Indoor Air," *Indoor and Ambient Air Quality*, R. Perry and P. Kirk (eds.). London, Selper Ltd., 99-112, 1988.

(16) Sterling, T. and Mueller, B., "Concentrations of Nicotine, RSP, CO and CO_2 in Nonsmoking Areas of Offices Ventilated by Air Recirculated from Smoking Designated Areas," *Am Ind Hyg Assoc J* 49(9): 423-426, 1988.

(17) Cox, B. and Whichelow, M., "Carbon Monoxide Levels in the Breath of Smokers and Nonsmokers: Effect of Domestic Heating Systems," *J Epidemiol Community Health* 39: 75-78, 1985.

(18) Duncan, D. and Greavey, P., "Passive Smoking and Uptake of Carbon Monoxide in Flight Attendants," *JAMA* 251(20): 120-121, 1984.

(19) Girman, J. and Traynor, G., "Indoor Concentrations," *J Air Pollut Control Assoc* 33(2): 89, 1983.

(20) Yocom, J., "Indoor Concentrations," *J Air Pollut Control Assoc* 33(2): 89, 1983.

(21) Nitta, H., et al., "Measurements of Indoor Carbon Monoxide Levels Using Passive Samplers in Korea," *Indoor Air '90: Proceedings of the Fifth International Conference on Indoor Air Quality and Climate*, Toronto, Canada, Volume 1, 77-82, July 29-August 3, 1990.

(22) Sterling, T., et al., "Environmental Tobacco Smoke and Indoor Air Quality in Modern Office Work Environments," *Journal of Occupational Medicine* 29(1): 57-62, 1987.

(23) Carson, J. and Erikson, C., "Results from Survey of Environmental Tobacco Smoke in Offices in Ottawa, Ontario," *Environ Technol Letters* 9: 501-508, 1988.

(24) Oldaker, G., et al., "Results From Surveys of Environmental Tobacco Smoke in Restaurants," *Indoor Air Quality*, H. Kasuga (ed.), Berlin, Heidelberg, Springer-Verlag, 99-104, 1990.

(25) Ogden, M. and Maiolo, K., "Collection and Analysis of Solanesol as a Tracer of Environmental Tobacco Smoke (ETS)," *Indoor and Ambient Air Quality*, R. Perry and P. Kirk (eds.). London, Selper Ltd., 77-88, 1988.

(26) Proctor, C., "The Analysis of the Contribution of ETS to Indoor Air," *Indoor and Ambient Air Quality*, R. Perry and P. Kirk (eds.), London, Selper Ltd., 57-66, 1988.

(27) Eatough, D., et al., "Assessing Exposure to Environmental Tobacco Smoke," *Indoor and Ambient Air Quality*, R. Perry and P. Kirk (eds.), London, Selper Ltd., 131-140, 1988.

(28) Proctor, C., et al., "Measurements of Environmental Tobacco Smoke in an Air-Conditioned Office Building," *Environ Technol Letters* (10): 1003-1018, 1989.

(29) Proctor, C., "A Multi-Analyte Approach to the Measurement of Environmental Tobacco Smoke," *Indoor Air Quality and Ventilation*, F. Lunau and G. Reynolds (eds.), London, Selper Ltd, 427-436, 1990.

(30) Oldaker, G. and Conrad, F., "Estimation of the Effect of Environmental Tobacco Smoke on Air Quality Within Passenger Cabins of Commercial Aircraft," *Environ Sci Technol* 21: 994-999, 1987.

(31) Hinds, W. and First, M., "Concentrations of Nicotine and Tobacco Smoke in Public Places," *New Eng Journal of Medicine* 292(16): 844-845, 1975.

(32) Badre, R., et al., "Pollution Atmospherique par la Fumee de Tabac (Atmospheric Pollution by Smoking)," *Ann Pharm Fr* 36(9-10): 443-452, 1978. Translation.

(33) Jenkins, R., et al., "Development and Application of a Thermal Desorption-Based Method for the Determination of Nicotine in Indoor Environments," *Indoor and Ambient Air Quality*, R. Perry and P. Kirk (eds.), London, Selper Ltd., 557-566, 1988.

(34) Muramatsu, M., et al., "Estimation of Personal Exposure to Tobacco Smoke with a Newly Developed Nicotine Personal monitor," *Environ Res* 35: 218-227, 1984.

(35) Muramatsu, M., et al., "Estimation of Personal Exposure to Ambient Nicotine in Daily Environment," *Arch Occup Environ Health* 59: 545-550, 1987.

(36) Thompson, C., et al., "A Thermal Desorption Method for the Determination of Nicotine in Indoor Environments," *Environ Sci Technol* 23: 429-435, 1989.

(37) Foliart, D., et al., "Passive Absorption of Nicotine in Airline Flight Attendants," *New England Journal of Medicine* 308(18): 1105, 1983.

(38) Stewart, R., "The Effects of Low Concentrations of Carbon Monoxide in Man," *Environmental Tobacco Smoke Effects on the Nonsmoker: Report from a Workshop*, R. Rylander (ed.), Published in *Scand J Respir Dis*, Suppl. 91: 56-62, 1974.

(39) Wade, W., "A Study of Indoor Air Quality," *J Air Pollut Control Assoc* 25(9): 933-939, 1975.

(40) Yocom, J., "Indoor-Outdoor Air Quality Relationships," *J Air Pollut Control Assoc* 32(5): 500-520, 1982.

(41) Turner, S., et al., "The Measurement of Environmental Tobacco Smoke in 585 Office Environments," Presentation at *ISEA* Meeting, Atlanta, GA., November, 1991.

(42) Sterling, T., "ETS Concentrations Under Different Conditions of Ventilation and Smoking Regulation," *Indoor and Ambient Air Quality*, R. Perry and P. Kirk (eds.), London, Selper Ltd., 89-98, 1988.

(43) McAughey, J., et al., "Risk Assessment of Exposure to Indoor Air Pollutants," *Env Int* (11): 295-302, 1990.

(44) Good, B., et al., "Effect of Cigarette Smoking on Residential NO_2 Levels," *Environ Int* 8: 167-175, 1982.

(45) Godish, T., "Formaldehyde Exposures from Tobacco Smoke: A Review," *AJPH* 79(8): 1044-1045, 1989.

(46) Stehlik, G., et al., "Concentration of Dimethylnitrosamine in the Air of Smoke-Filled Rooms," *Ecotoxicol Environ Safety* 6: 495-500, 1982.

(47) Sega, K. and Fugas, M., "Nitrogen Dioxide Concentrations in Residences," *Indoor and Ambient Air Quality*, R. Perry and P. Kirk (eds.), London, Selper Ltd., 493-496, 1988.

(48) Shimizu, Y., et al., "Influence of Indoor Air Pollution on NO2 Personal Exposure Levels of Schoolchildren," *Present and Future of Indoor Air Quality*, C. Bieva, et al. (eds.), Brussels, Elsevier Science Publishers, 337-345, 1989.

(49) Bayer, C. and Black, M., "Thermal Desorption/Gas Chromatographic/Mass spectrometric Analysis of Volatile Organic Compounds in the Offices of Smokers and Nonsmokers," *Biomed and Envir Mass Spect* 14(8): 363-367, 1987.

(50) Adlkofer, F., et al., "Significance of Exposure to Benzene and Other Toxic Compounds Through Environmental Tobacco Smoke," *J Cancer Res Clin Oncol* (116): 591-598, 1990.

(51) Hugod, C., et al., "Exposure of Passive Smokers to Tobacco Smoke Constituents," *Int Arch Occup Environ Health* (42): 21-29, 1978.

(52) Coultas, D., et al., "Questionnaire Assessment of Lifetime and Recent Exposure to Environmental Tobacco Smoke," *American Journal of Epidemiology* 130(2): 338-347, 1989.

Coultas, D., et al., "Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home," *American Review of Respiratory Disease* 142: 602-606, 1990.

(53) Coultas, D., et al., "A Personal Monitoring Study to Assess Workplace Exposure to Environmental Tobacco Smoke," *American Journal of Public Health* 80(8): 988-990, 1990.

(54) Kabat, G. and Wynder, E., "Lung Cancer in Nonsmokers," *Cancer* 53(5): 1214-1221, 1984.

Garfinkel, L., Auerbach, O. and Joubert, L., "Involuntary Smoking and Lung Cancer: A Case-Control Study," *Journal of the National Cancer Institute* 75(3): 463-469, 1985.

Wu, A., Henderson, B.E., Pike, M.C. and Yu, M.C., "Smoking and Other Risk Factors for Lung Cancer in Women," *Journal of the National Cancer Institute* 74(4): 747-751, 1985.

Janerich, D., Thompson, W.D., Varela, L.R., Greenwald, P., Chorost, S., Tucci, C., Zaman, M.B., Melamed, M.R., Kiely, M. and McKneally, M.F., "Lung Cancer and Exposure to Tobacco Smoke in the Household," *New England Journal of Medicine* 323: 632-636, 1990.

Brownson, R.C., Alavanja, M.C.R., Hock, E.T., and Loy, T.S., "Passive Smoking and Lung Cancer in Nonsmoking Women," *American Journal of Public Health* 82(11): 1525-1530, 1992.

Stockwell, H.G., Goldman, A.L., Lyman, G.H., Noss, C.I., Armstrong, A.W., Pinkham, P.A., Candelora, E.C., and Brusa, M.R., "Environmental Tobacco Smoke and Lung Cancer Risk in Nonsmoking Women," *Journal of the National Cancer Institute* 84(18): 1417-1422, 1992.

Kabat, G.C., "Epidemiologic Studies of the Relationship Between Passive Smoking and Lung Cancer," *Toxicology Forum: 1990 Annual Winter Meeting*, Washington, D.C., 187-199, February 19-21, 1990.

Fontham, E.T.H., Correa, P., Wu-Williams, A., Reynolds, P., Greenberg, R.S., Buffler, P.A., Chen, V.W., Boyd, P., Alterman, T., Austin, D.F., Liff, J. and Greenberg, S.D., "Lung Cancer in Nonsmoking Women: A Multicenter Case-Control Study," *Cancer Epidemiology, Biomarkers & Prevention* 1: 35-43, 1991.

Lee, P.N., Chamberlain, J. and Alderson, M.R., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," *British Journal of Cancer* 54: 97-105, 1986.

Svensson, C., Pershagen, G. and Klominek, J., "Smoking and Passive Smoking in Relation to Lung Cancer in Women," *Acta Oncologica* 28(5): 623-639, 1989.

Kalandidi, A., Katsouyanni, K., Voropoulou, N., Bastas, G., Saracci, R. and Trichopoulos, D., "Passive Smoking and Diet in the Etiology of Lung Cancer Among Non-Smokers," *Cancer Causes and Control* 1: 15-21, 1990.

Koo, L.C., Ho, J.H.-C., Saw, D. and Ho, C.Y., "Measurements of Passive Smoking and Estimates of Lung Cancer Risk Among Non-Smoking Chinese Females," *International Journal of Cancer* 39: 162-169, 1987.

Shimizu, H., Morishita, M., Mizuno, K., Masuda, T., Ogura, Y., Santo, M., Nishimura, M., Kunishima, K., Karasawa, K., Nishiwaki, K., Yamamoto, M., Hisamichi, S. and Tominaga, S., "A Case-Control Study of Lung Cancer in Non-smoking Women," *Tohoku Journal of Experimental Medicine* 154: 389-97, 1988.

Wu-Williams, A.H., Dai, X.D., Blot, W., Xu, Z.Y., Sun, X.W., Xiao, H.P., Stone, B.J., Yu, S.F., Feng, Y.P., Ershow, A.G., Sun, Jr., Fraumeni, J.F. and Henderson, B.E., "Lung Cancer among Women in North-East China," *British Journal of Cancer* 62: 982-987, 1990.

(55) Dobson, A.J., Alexander, H.M., Heller, R.F. and Lloyd, D.M., "Passive Smoking and the Risk of Heart Attack or Coronary Death," *The Medical Journal of Australia* 154: 793-797, 1991.

Helsing, K.J., Sandler, D.P., Comstock, G.W. and Chee, E., "Heart Disease Mortality in Nonsmokers Living With Smokers," *American Journal of Epidemiology* 127(5): 915-922, 1988.

Hirayama, T., "Lung Cancer in Japan: Effects of Nutrition and Passive Smoking," *Lung Cancer: Causes and Prevention*, M. Mizell and P. Correa (eds.), New York, Verlag Chemie International Chapter 14, 175-195, 1984.

Lee, P.N., Chamberlain, J. and Alderson, M.R., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," *British Journal of Cancer* 54: 97-105, 1986.

Svendsen, K.H., Kuller, L.H., Martin, M.J. and Ockene, J.K., "Effects of Passive Smoking in the Multiple Risk Factor Intervention Trial," *American Journal of Epidemiology* 126(5): 783-795, 1987.

(56) White, J.R. and Froeb, H.F., "Small-Airways Dysfunction in Nonsmokers Chronically Exposed to Tobacco Smoke," *The New England Journal of Medicine* 302 (13): 720-723, 1980.

Kentner, M., Triebig, G. and Weltle, D., "The Influence of Passive Smoking on Pulmonary Function - A Study of 1,351 Office Workers, *Prevention Medicine* 13(6): 656-669, 1984.

Kentner, M. and Weltle, D., "Passive Tobacco Smoke Inhalation and Lung Function in Adults," *Indoor and Ambient Air Quality*, R. Perry and P. Kirk (eds.), London, Selper Ltd., 232-241, 1988.

Kentner, M. and Weltle, D., "Are There Any Impairments of Maximal Expiratory Flow-Volume Curves by Passive Smoking?" *Indoor Air Quality*, H. Kasuga (ed.), Berlin, Heidelberg, Springer-Verlag, 153-166, 1990.

Kentner, M., Weltle, D. and Valentin, H., "Passive Smoking and Lung Function in Adults," *Arbeitsmedicine Sozialmedicine Praventivmedicine* (24): 8-13, 1989.

White, J.R., Froeb, H.F. and Kulik, J.A., "Respiratory Illness in Nonsmokers Chronically Exposed to Tobacco Smoke in the Work Place," *Chest* 100(1): 39-43, 1991.

(57) Adlkofer, F., Scherer, G. and Weimann, H., "Small-Airways Dysfunction in Passive Smokers," *New England Journal of Medicine* 303(7): 392, 1980.

Huber, G., "Small-Airways Dysfunction in Passive Smokers," *New England Journal of Medicine* 303(7): 392, 1980.

Freedman, A., "Small-Airways Dysfunction in Passive Smokers," *New England Journal of Medicine* 303(7): 393, 1980.

Aviado, D.,."Small-Airways Dysfunction in Passive Smokers," *New England Journal of Medicine* 303(7): 393, 1980.

Lee, P.N., "Passive Smoking," *Food Chemistry and Toxicology* 20: 223-229, 1982.

White, J. and Froeb, H., "Small-Airways Dysfunction in Passive Smokers," *New England Journal of Medicine* 303(7): 393-394, 1980.

Lebowitz, M., "Forum: Second Hand Smoke — How Dangerous?," Presentation to the American Lung Association/ American Thoracic Society Annual Meeting, Los Angeles, California, May 17, 1982.

Fountain, L.H., Statement Re: "White-Froeb Study Discredited by Scientists," *U.S. Congressional Record*, 97th Congress, 2nd Session, E5252-5254, December 16, 1982.

Lebowitz, M.,"Influence of Passive Smoking on Pulmonary Function: A Survey," *Preventive Medicine* 13(6): 645-655, 1984.

Laurent, A.M., Courtois, Y.A., Pretet, S. and Claude,, J.R., "Evaluation of Exposure to Ambient Tobacco Smoke: A Few Concrete Examples Concerning the Value of Biological Atmospheric Indicators," *Present and Future of Indoor Air Quality*, C.J. Bieva, Y. Courtois, M. Govaerts (eds.), Amsterdam, Excerpta Medica, 103-110, 1989.

Graham, N.M.H., "The Epidemiology of Acute Respiratory Infections in Children and Adults: A Global Perspective," *Epidemiologic Reviews* 12: 149-178, 1990.

Witorsch, P., "Health Effects of Environmental Tobacco Smoke," *Toxicology Forum: 1990 Annual Winter Meeting*, Washington D.C., 212, February 19-21, 1990.

U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, *Report of Workshop on Respiratory Effects of Involuntary Smoke Exposure: Epidemiologic Studies, May 1-3, 1983*, December, 1983.

(58) Dahms, T.E., Bolin, J.F. and Slavin, R.G., "Passive Smoking Effects on Bronchial Asthma," *Chest* 80(5): 530-534, 1981.

Pimm, P.E., Shephard, R.J. and Silverman, F., "Physiological Effects of Acute Passive Exposure to Cigarette Smoke in Asthmatics," *Federal Proceedings* 36(3): 606, 1977. Abstract.

Shephard, R.J., Collins, R. and Silverman, F., "'Passive Exposure to Asthmatic Subjects to Cigarette Smoke," *Environmental Research* 20: 392-402, 1979.

Knight, A. and Breslin, A.B.X., "Passive Cigarette Smoking and Patients with Asthma," *The Medical Journal of Australia* 142: 194-195, 1985.

Ing, A. and Breslin, A.B.X., "The Effect of Passive Cigarette Smoking and Asthmatic Patients," *Proceedings*, The Thoracic Society of Australia, 543, October, 1983. Abstract.

Wiedemann, H.P., Mahler, D.A., Loke, J., Virgulto, J.A., Snyder, P. and Matthay, R.A., "Acute Effects of Passive Smoking on Lung Function and Airway Reactivity in Asthmatic Subjects," *Chest* 89(2): 180-184, 1986.

Stankus, R.P., Menon, P.K., Rando, R.J., Glindmeyer, H., Salvaggio, J.E. and Lehrer, S.B., "Cigarette Smoke-Sensitive Asthma: Challenge Studies," *Journal of Allergy and Clinical Immunology* 82: 331-338, 1988.

Lebowitz, M., "The Effects of Environmental Tobacco Smoke Exposure and Gas Stoves on Daily Peak Flow Rates in Asthmatic and Non-Asthmatic Families," *ETS-Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels*, R. Rylander, Y. Peterson and M.-C. Snella (eds.), Published simultaneously in *European Journal of Respiratory Diseases*, Supplement No. 133, Vol. 65, 90-97, 1984.

Bailey, W.C., Richards, J.M., Manzella, B.A., Brooks, C.M., Windsor, R.A. and Soong, S.J., "Characteristics and Correlates of Asthma in a University Clinic Population," *Chest* 98(4): 821-828, 1990.

Magnussen, H., "The Effect of Passive Smoking on Airway Tone and Responsiveness in Children and Adults with Bronchial Asthma," *The Toxicology Forum: 1990 European Meeting*, Budapest, Hungary. June 18-22, 1990: 202-205.

(59) Skov, P., et al., "Influence of Personal Characteristics, Job-Related Factors and Psychosocial Factors on the Sick Building Syndrome," *Scand J Environ Health* 15: 286-295, 1989.

(60) Hawkins, L. and Wang, T., "The Office Environment and the Sick-Building Syndrome," *Healthy Buildings* 365-371, 1991.

(61) Colligan, M., "The Psychological Effects of Indoor air Pollution," *Bulletin of the New York Academy of Medicine* 57: 1014-1026, 1981.

(62) Helsing, K.J., et al., "Cure of a Sick Building: A Case Study," *Environmental International* 15: 107-114, 1989.

(63) Hanssen, S. and Mathisen, H., "Sick Building — A Ventilation Problem?," *Indoor Air '87, Proceedings of the 4th International Conference on Indoor Air Quality and Climate, Berlin (West), 17-21 August 1987*, Institute of Water, Soil and Air Hygiene 3: 357-361.

(64) Beller, M. and Middaugh, J., "Results of an Indoor Air Pollution Investigation," *Alaska Medicine* 31(4): 148-155, 1989.

(65) Thompson, R., et al., "HVAC Retrofit for Healthy Schools," *IAQ 91: Healthy Buildings*, ASHRAE, 230-235, 1991.

(66) Downing, C., "Operation and Maintenance for Quality Indoor Air," *IAQ 91: Healthy Buildings*, ASHRAE, 372-374, 1991.

(67) Nelson, C., et al., "EPA's Indoor Air Quality and Work Environment Survey: Relationships of Employees' Self-Reported Health Symptoms With Direct Indoor Air Quality Measurements," *IAQ 91: Healthy Buildings*, ASHRAE, 22-32, 1991.

(68) Walkinshaw, D., "Investigating Indoor Air Quality Complaints: Exploratory Measurements of Air Exchange Rates, Volatile Organic Compounds and Fungi," *The Practitioner's Approach to Indoor Air Quality Investigations, Proceedings of the Indoor Air Quality International Symposium*, D. Weekes and R. Gammage (eds.), American Industrial Hygiene Association, 35-49, 1989.

(69) American Society of Heating, Refrigerating and Air-Conditioning Engineers, "ASHRAE Standard 62-1989, Ventilation for Acceptable Indoor Air Quality," Atlanta, ASHRAE Publications, 1989.

(70) Goodfellow, H. and J. Wyatt, "Critical Review of Ventilation Contaminants in Indoor Air," *Indoor Air Quality and Ventilation*, F. Lunau and G. Reynolds (eds.), London, Selper Ltd., 95-104, 1990.

(71) Binnie, P., "The Role of Ventilation in Controlling the Quality of Indoor Air, Including ETS," *Other People's Tobacco Smoke*, A. Armitage (ed), Beverly, East York, United Kingdom, Galen Press, 159-172, 1991.

(72) Burroughs, H., "ASHRAE: Addressing the Indoor Air Quality Challenge With Energy Conscious Design," *Indoor and Ambient Air Quality*, R. Perry and P. Kirk (eds), London, Selper Ltd., 530-535, 1988.

(73) Menzies, R., et al., "The Effect of Varying Levels of Outdoor Ventilation on Symptoms of Sick Building Syndrome," *IAQ 91: Healthy Buildings*, ASHRAE, 90-96, 1991.

(74) Nagda, N., et al., "Effect of Ventilation Rate in a Health Building," *IAQ 91: Healthy Buildings*, ASHRAE, 101-107, 1991.

(75) "IAQU Case Study: Investigation Employee Complaints of 'Bug Bites,'" *Indoor Air Quality Update* 4(10): 15-19, 1991.

(76) "Case History: A School's Indoor Air Pollution Witch-Hunt?," *Healthy Buildings International* 6-15, September/October, 1991.

(77) Turner, W., et al., "Diagnostics and Remediation for health Schools," *IAQ 91: Healthy Buildings*, ASHRAE, 225-227, 1991.

(78) Pedelty, J. and Holcomb, C., "A Computer Simulation of Indoor Air Quality Which Models Changes in Point Sources and Ventilation," *Environmental Technology* 11: 1053-1062, 1990.

(79) Morey, P. and Singh, J., "Indoor Air Quality in Nonindustrial Occupational Environments," *Patty's Industrial Hygiene and Toxicology*, Fourth Edition (1)(A), G. Clayton and F. Clayton (eds.), John Wiley and Sons, Inc., 531-594, 1991.

(80) Eto, J.H., Myer, C., "The HVAC Costs of Increased Fresh Air Ventilation Rates in Office Buildings," *ASHRAE Transactions*, 94(2), 1988.

(81) Eto, J.H., Meyer, C., "The HVAC Costs of Fresh Air Ventilation," *ASHRAE Journal*, 30(8): 31-35, 1988.

(82) Eto, J., "The Costs of Increased Fresh Air Ventilation Rates in Office Buildings Part 2," *Indoor Air '90*, Toronto, Canada, 53-58, 1990.

(83) The Sheet Metal and Air Conditioning Contractor's National Association, Statement on H1066 "The Indoor Air Quality Act of 1991," to the House Science, Space and Technology Committee, Environment Subcommittee, May 9, 1991.

(84) Ventresca, J., "Operation and Maintenance for Indoor Air Quality: Implications from Energy Simulations of Increased Ventilation," *IAQ 91: Healthy Buildings*, ASHRAE Publications, 375-378, 1991.

(85) Binnie, P., "The Role of Ventilation in Controlling the Quality of Indoor Air, Including ETS," *Other People's Tobacco Smoke*, A. Armitage (ed.), East Yorkshire, United Kingdom, Galen Press, 159-172, 1991.

(86) Carpenter, D. and Poitrast, B., "Recommended Carbon Dioxide and Relative Humidity Levels for Maintaining Acceptable Indoor Air Quality," USAF Occupational and Environmental Health Laboratory, Brooks AFB, Texas: October, 1990.

(87) Miller, R., *Indoor Air Quality*, Norcross, GA, SEAI Technical Publications, 145: 1991.

(88) United Press International, "Citing Poor Indoor Air Quality for Lost . . .," December 18, 1991.

(89) Vaughan, W. and Hammond, K., "Impact of 'Designated Smoking Area' Policy on Nicotine Vapor and Particle Concentrations in a Modern Office Building," *J Air Waste Manage Assoc* 40: 1012-1017, 1990.

(90) Hedge, A., et al., "Building Ventilation and Smoking Policy Effects on Indoor Air Quality and Employee Comfort and Health," *Indoor Air '90*, Toronto, Canada, 739-744, July 29-August 3, 1990.

(91) Hedge, A., et al., "The Effects of Smoking Policy on Indoor Air Quality and Sick Building Syndrome in 18 Air-Conditioned Offices," *IAQ 91: Healthy Buildings*: 151-159, 1991.

(92) Lee, H., et al., "Impact of a New Smoking Policy on Office Air Quality," *Indoor Air Quality in Cold Climates: Hazards and Abatement Measures*, D. Walkinshaw (ed.), 307-313, 1985.

(93) Drake, J. and Johnson, D., "Measurements of Certain Environmental Tobacco Smoke Components on Long-Range Flights," *Aviation, Space and Environmental Medicine* 61: 531-542, 1990.

(94) Oldaker, G., et al., "Estimation of Effect of Environmental Tobacco Smoke on Air Quality Within Passenger Cabins of Commercial Aircraft," *Indoor Air Quality and Ventilation*, Selper Ltd., London, 447-454, 1990.

(95) Nagda, N., et al., "Airliner Cabin Environment: Contaminant Measurements, Health Risks, and Mitigation Options," Final Report to the Department of Transportation. DOT-P-15-89-5. U.S. Government Printing Office, December, 1989.

(96) Proctor, C., "A Study of the Atmosphere in London Underground Trains Before and After the Ban on Smoking," *Toxicology Letters, Proceedings of the International Experimental Toxicology Symposium on Passive Smoking*, E. Mohtashamipur (ed.). Amsterdam, Elsevier, 131-134, October 23-25, 1986.

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APPENDIX B

CRITIQUE OF REPACE/LOWREY'S

"ENFORCEABLE IAQ STANDARD"

A CRITIQUE OF:

"AN ENFORCEABLE INDOOR AIR QUALITY STANDARD FOR ENVIRONMENTAL TOBACCO SMOKE IN THE WORKPLACE,"

by JAMES L. REPACE AND ALFRED H. LOWREY,

Risk Analysis 13(4): 463-474, 1993

Summary:

In their paper, Repace and Lowrey claim to have developed "a model which permits using atmospheric nicotine measurements to estimate nonsmokers' ETS lung cancer risks in individual workplaces for the first time." The model is a modification and extension of previous exposure and risk models developed by the authors.[1-2] Both models were heavily criticized in the scientific literature.[3-12]

The report presents no new data on workplace exposures to ETS, and the model that is developed to assess exposure and risk does not utilize available epidemiologic data or actual exposure data from the published literature. The available epidemiologic data on the workplace provide virtually no support to the claim that ETS exposures are associated with an increased risk of lung cancer for nonsmokers. Moreover, actual measurements of constituents of ETS in the air of offices, restaurants and public places are five to ten times lower than the exposure estimates generated by Repace and Lowrey's theoretical model.

The estimates for "acceptable" and "obvious" risks proposed by the authors are based upon erroneous exposure estimates for ETS-related respirable suspended particulate (RSP) (smoke particles), nicotine and cotinine, a substance converted from nicotine by the body. The calculated "acceptable risk" for airborne RSP attributable to ETS is 1,000 times lower than the permissible exposure levels set by the World Health Organization, the U.S. EPA and Health and Welfare Canada; the calculated "acceptable risk" level is also well below background levels reported for RSP in smoke-free environments. The suggested permissible airborne exposure level for nicotine is so minuscule that it is below detection limits for sophisticated air monitoring devices, and the level of "obvious risk" calculated for cotinine levels in the body fluids of nonsmokers is attainable by the ingestion of common foods -- potatoes, tomatoes, eggplant and fruits -- in the absence of any exposure to ETS.

Background

A model that generates "acceptable" levels of exposure for various ETS constituents that are lower than the detection limits of sophisticated air monitoring devices, or one that provides estimates of "obvious risk" that are surpassed in individuals who are not even exposed to ETS, must be seriously questioned. The model's principal shortcoming is found in the estimates generated for nonsmoker exposure to various ETS

constituents in the workplace. The model-generated estimates of exposure do not track reality and are not remotely similar to the available empirical data regarding actual workplace exposure to ETS constituents.

In 1980, Repace and Lowrey published a description of a model for predicting and estimating ETS exposures based on the use of respirable suspended particulate (RSP) as a marker for ETS.[1] The authors also sampled the air of meeting and game rooms, bars, sandwich shops and similar venues for RSP. They claimed that the average level of RSP measured in the various locations verified their predictive model (approximately 250 micrograms per cubic meter of air (ug/m^3)).[1,2]

The sampling procedures used by the authors were challenged, as was their assumption that all RSP in the air is attributable to ETS.[3-6] Dust indoors contributes substantially to RSP. Chemical analyses have been developed for estimating the relative contribution of ETS to total RSP indoors. Field studies indicate that ETS-RSP comprises from 10% to 50% of total indoor air RSP, and typically contributes 25 to 35% of the RSP present in an environment in which smoking takes place.[13]

Actual measurements of RSP in hundreds of offices and similar workplaces reveal that source-apportioned RSP due to ETS is

typically 5 to 10 times lower than the "average" level reported by Repace and Lowrey.[14-19]

- One recent investigation reported that average levels of RSP in 330 offices in which smoking was permitted was 46 micrograms per cubic meter (ug/m^3), compared with an average of 20 ug/m^3 reported for 254 nonsmoking offices;[19]

- Four studies on the measurement of RSP from ETS in the workplace were reviewed by scientists from Oak Ridge National Laboratories (ORNL) in their 1992 monograph on the chemistry and measurement of ETS.[13] The four studies reported average RSP concentrations from ETS of: 27 ug/m^3 for 131 offices; 32 ug/m^3 for 22 offices; 28 ug/m^3 for 194 offices and 44 ug/m^3 for 31 offices;

- Authors of a 1988 survey of 31 offices in Ottawa, Canada, cited by Repace and Lowrey (Reference No. 70), noted that: "based on the results of this survey, the average office worker was exposed to 0.0039 cigarette equivalent per hour (using nicotine as a marker), 0.0010 cigarette equivalent per hour [for ETS-related RSP]. . . the time for

exposure to 1 cigarette equivalent would have been 260 hours (using nicotine) or 1,000 hours [for ETS-related RSP]."[14]

The overestimation of RSP attributable to ETS by the authors' 1980 exposure model was applied to their risk assessment model published in 1985.[2] In their 1985 paper, the 250 ug/m^3 "average" exposure of RSP estimated by the authors' 1980 exposure model generates an estimated average daily "lung exposure" (dose) of 1430 ug RSP. (The "dose" function is calculated by the equation: exposure (250 ug/m^3) (x) duration (8 hours) (x) rate of respiration (1 m^3/hour).*

- The risk model was criticized because its assumptions for exposure and dose were not based on actual measurements. One commenter observed that actual exposure measurements reported by other

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*. By comparing the rate of lung cancer reported in a single study on Seventh Day Adventists (presumed to be unexposed to ETS) with that reported for a population of non-Seventh Day Adventists (who presumably were exposed to ETS), the authors report a mortality rate for non-Seventh Day Adventists that is 2.4 times that of the Seventh Day Adventist group. Extrapolated to the general population of an estimated 63 million nonsmokers in the U.S., the mortality rate generates an estimate of 4,700 lung cancer deaths per year. This is an excess mortality rate of 7.4 lung cancer deaths per 100,000, or 5 lung cancer deaths per 1 milligram (1000 ug) of RSP per day (derived by dividing 7.4 lung cancer deaths by 1.43 mg (1430 ug) of daily RSP "lung exposure.")

researchers ranged from "10-to-100-fold less than that in the Repace and Lowrey model";[9]

- Other scientists suggested that the author's model used erroneous and "unrealistic assumptions" that resulted in overestimations of risk and exposure.[7,8,10,12] In particular, one analysis demonstrated that, depending upon which assumptions were selected, model-generated estimates of exposure and risk could vary as much as 300-fold;[8]

- The estimated "lung exposure" of ETS-related RSP generated by the Repace-Lowrey model does not resemble other estimates published in the scientific literature.[8,20-24] This is because the Repace-Lowrey model employs unrealistically high levels of average exposures to RSP, and because the model fails to factor in important variables such as particle behavior and deposition, lung retention and clearance mechanisms;[20]

- Based upon the above-mentioned factors and upon realistic exposure measurements, several authors have independently estimated levels of ETS-RSP uptake by nonsmokers to approximate 0.02% (1/200 of

one percent) that of the particulate uptake for an active smoker;[8,21-23]

- Other scientists report that "the lung cell doses for average ETS-exposed nonsmokers are probably between 1/10,000 and 1/100,000 of equivalent cell doses for average mainstream active smokers. In practical terms, this implies an annual retained dose of tobacco smoke components equivalent to far less than the dose from the active smoking of one cigarette somehow evenly dispersed over one year period" [emphasis added];[20]

- Another researcher recently reviewed the available published data on exposure to ETS constituents, including RSP from ETS.[24] Based upon actual levels of RSP averaged over a number of studies in the workplace environment, the researcher calculated a "retained dose" for a nonsmoker that approximated 2/5 to 1/2 of a single cigarette (equivalent) over a year of exposure to ETS. [emphasis added] He remarked: "Toxicologically, it does not make any sense that retained doses of these very small amounts of respirable particulate from ETS would result in disease."

The Repace-Lowrey Nicotine Model

The model described in Repace and Lowrey's recent paper converts the authors' previous models based on estimated exposures to RSP into a single model for estimating risk and exposure that is based upon nicotine (and its metabolite, cotinine). This exercise was undertaken because, according to Repace and Lowrey, "an indoor air quality standard based upon RSP. . . would be difficult to enforce." (p. 464) RSP, the authors now apparently realize, "is not unique to ETS." (p. 464) The authors also argue that "quantification of ETS exposure and risk for regulatory purposes must be predicated upon substances uniquely associated with tobacco combustion, such as nicotine in workplace air." The authors believe that nicotine, and its metabolite, cotinine, "are the best available markers for ETS exposure and dose," and "therefore also serve as the most suitable markers for the carcinogenic effect of ETS," even though the authors concede nicotine and cotinine's "apparent lack of carcinogenic activity." (p. 464)

The first step in Repace and Lowrey's attempt to convert the RSP-based exposure model to one based upon nicotine requires the assumption that there is a constant ratio between airborne RSP and airborne nicotine. A constant ratio would make extrapolation from one model to another possible. Repace and Lowrey suggest a constant ratio of 10:1 for RSP and nicotine. Contrary to Repace

and Lowrey, the existence of such a ratio is an open question according to the scientific literature.[25] However, of critical importance is Repace and Lowrey's estimate for exposure to nicotine. The estimate is derived by dividing the "lung exposure" estimate of 1430 ug/day RSP by 10 (the 10:1 ratio) to yield an estimated "lung exposure" of 143 ug/day nicotine. Unfortunately, the authors do not appear aware of the fact that nicotine appears in the gas-phase of ETS and therefore would exhibit kinetic and depositional properties that are different from RSP (particle-phase substances). Moreover, the "lung exposure" estimate of 143 ug/day for nicotine represents a gross over-estimation when compared to actual nicotine measurements in the workplace reported in the scientific literature. For example:

- In the Canadian workplace study cited by Repace and Lowrey (Reference No. 70), the researchers measured nicotine in the air of offices and restaurants in Ottawa, Canada.[14] They reported average nicotine exposure levels equivalent to 3/100 of a cigarette per 8 hour workday in an office, and to 3/1000 cigarette exposure during a 1 hour meal in a restaurant;

- In a study of over 3,000 travel, work, home and leisure locations in the U.K., investigators

reported nicotine levels that were below detection limits for three-quarters of all sites, even though smoking was known to have occurred in nearly half of those locations;[26]

- In another study cited by Repace and Lowrey (Reference No. 71), average nicotine levels reported for 156 office samples and 170 restaurant samples were 4.8 and 5.1 ug/m^3, respectively.[15] According to the study's authors, "estimated mean exposure for an 8-hour workday in an office is 0.02 cigarette equivalent and for a 1-h meal in a restaurant, 0.003 cigarette equivalent";

- In a recent study of 585 offices, researchers reported nicotine levels between zero and 2.5 ug/m^3 in nearly all of the nonsmoking offices sampled. Nicotine levels averaged .02 ug/m^3 for all nonsmoking offices, and 6.7 ug/m^3 for smoking offices;[19]

- Canadian researchers reported nicotine levels of 1 ug/m^3 or less in nonsmoking offices that received recirculated air from designated smoking areas.[27] This is an exposure equivalent for nicotine of a

little more than 1/1000 of a single cigarette. Using Repace and Lowrey's over-simplified model for the determination of "lung exposure" to nicotine, it would take about 3 hours for a nonsmoker to "absorb" 1 ug of nicotine. Expressed another way, it would take over 400 continual hours of such exposure -- 10 weeks of work -- to be exposed to the level generated by the Repace and Lowrey model for a single day of exposure to nicotine (143 ug)!

The Repace-Lowrey Cotinine Model

In the next step of their analysis, Repace and Lowrey attempt to verify the nicotine "exposure" model by comparing estimates of exposure to reported levels of cotinine in body fluids of nonsmokers. An estimative model for cotinine is developed by the authors, and the predictions generated by the model for cotinine are compared with levels of cotinine actually measured in several studies of nonsmokers.

Although Repace and Lowrey suggest that their model predictions for cotinine levels correlate with, and therefore support, the predictions of their nicotine "exposure" model, the exercise by the authors is not meaningful. That is because the so-called correlation between model-generated estimates for nicotine

in the air and cotinine levels in body fluids has no basis in reality -- the results for nicotine are not based upon actual ambient measurements.

A more fundamental flaw in Repace and Lowrey's analysis of cotinine follows from the authors' assumptions that: (1) cotinine is a reliable quantitative measure of ETS exposure; (2) airborne levels of nicotine can be correlated with body fluid levels of cotinine, and (3) body fluid levels of cotinine are determined solely by airborne levels of nicotine. None of these assumptions has been borne out in the scientific literature.

- Cotinine has never been demonstrated to be a reliable quantitative marker for ETS (or nicotine) exposure in nonsmokers. According to one of the reviewers of the present Repace-Lowrey study, (also cited in their paper (Reference No. 28)): "Within a given exposure level there was considerable variability in cotinine values. Cotinine was chosen as a biological marker of ETS exposure because it is specific to tobacco smoke. However, cotinine levels in body fluids may not only reflect environmental exposure to tobacco smoke, but also factors that influence uptake and metabolism of nicotine."[28] The authors conclude:

> The relatively modest correlation between reported ETS exposure and urinary cotinine indicated that other factors such as differing metabolic rates and body size may have a confounding effect on the relationship between cotinine levels and questionnaire measures of ETS exposure. In view of this finding, we would recommend against using cotinine levels as a strictly quantitative indicator of ETS.

- A concentration of cotinine at any given time depends not only upon the exposure and dose of nicotine, but also upon the rate of metabolic conversion of nicotine to cotinine in an individual, as well as upon the rate of elimination or clearance of cotinine from the body. Individuals metabolize nicotine in different ways at different times, and elimination and clearance rates for cotinine vary among individuals. Any single determination of a given cotinine level in the body fluid of an individual is therefore subject to physiological, pathological and genetic variabilities.[29-35] It is thus impossible to extrapolate, with any degree of confidence or reliability, from cotinine concentrations to nicotine exposure in the ambient air, given inter-individual variations in the metabolism and clearance of cotinine.

- Can ambient levels of nicotine be correlated with body fluid levels of cotinine, as assumed by Repace and Lowrey? According to researchers cited by Repace and Lowrey themselves, the answer is no. For example, Curvall and colleagues (Reference No. 46 in Repace and Lowrey) note in another study: "The pharmacokinetics of nicotine and cotinine have been evaluated in smokers and nonsmokers at concentrations usually achieved by smokers, and little is known about the kinetics of these compounds at concentrations found in nonsmokers exposed to environmental tobacco smoke nicotine. . . the suitability of cotinine as a marker of environmental tobacco smoke nicotine exposure has only been evaluated in field studies; no data are available on the relationship between low dose nicotine intake and cotinine concentrations in nonsmokers."[29]

In a series of studies by other authors cited by Repace and Lowrey (Reference No. 67), Coultas et al., compared ETS exposure measurements, questionnaire estimates of exposure and cotinine levels in nonsmokers.[36-38] They report:

> During one workshift, we obtained questionnaires on exposure, saliva and urine for cotinine, and personal air samples for respirable particles and nicotine. The levels of cotinine, respirable particles, and nicotine varied widely with self-reports of exposure to ETS.

- Idle of the United Kingdom wrote in 1989:[30]

> The complex of dynamic interactions which leads to a certain salivary or urinary concentration of cotinine at one point in time following exposure to a defined amount of airborne nicotine needs to be dissected. . . single point cotinine concentrations can give no more than a clue to a past exposure to pyridine alkaloids of unknown amount, at an unspecified time, by an unknown route of entry and from unknown origins.

- The assumption that cotinine levels in body fluids are the sole result of airborne nicotine exposures from ETS is undermined by a third area of research that has identified significant sources of nicotine in the common diet. According to a recent report by Domino, et al., trace levels of nicotine can be found in a number of human foods such as potatoes, tomatoes and eggplant.[39] The researchers report that their findings independently verify previous reports by other investigators.[40-42] Recorded levels of nicotine in various vegetables such as

cauliflower, eggplant, potatoes and tomatoes range from about 3 nanograms/gram to about 100 nanograms/gram -- where a nanogram is 1 billionth of a gram and 28 grams are equivalent to one ounce. If one assumes complete absorption of the nicotine from vegetables during ingestion, an individual would consume about 10 grams of eggplant, 65 grams of potatoes or 93 grams of tomatoes to obtain a 1 microgram dosage of nicotine. This translates into about one-third ounce of eggplant, five ounces of potato, or about eight and one-half ounces of ripe tomato to account for a 1 ug intake of nicotine. (A nonsmoker exposed to 1 ug/m^3 of nicotine in the air would take approximately three hours to "absorb" 1 ug.)

Similarly, Davis, et al. (1991) calculated a total of 8.8 ug intake of nicotine per day from the consumption of average quantities of the foods mentioned above.[42] This would result in a urinary cotinine concentration estimated at approximately 0.6 ng/ml. Maximum consumption of nicotine-containing foods could result in an estimated urinary cotinine concentration of 6.2 ng/ml. This range of values for cotinine due to diet is

comparable to levels reported in various studies for nonsmokers who are exposed to ETS.

Thus, cotinine is not a reliable quantitative measure of ETS exposure. This is because body fluid levels of cotinine cannot be attributed solely to nicotine in ETS, and because body fluid levels of cotinine do not correlate well with actual ambient air exposures to nicotine or with other ETS constituents.

Risk Estimates

Repace and Lowrey apply the exposure estimates generated by their particulate, nicotine and cotinine models to their previous estimates of excess risk purportedly due to ETS. The authors base their estimate of excess risk on the analysis of a single study which compared lung cancer mortality in Seventh Day Adventists with a group of non-Seventh Day Adventists.[2] The study did not assess ETS exposures. Rather, Repace and Lowrey assumed that Seventh Day Adventists are not exposed to ETS and that all individuals in the non-Seventh Day Adventist group are. The difference in the lung cancer mortality rate between the two groups was applied to the overall population of nonsmokers in the U.S. This generated an estimated risk of approximately 5,000 lung cancer deaths per year (5 lung cancer deaths/100,000/1,000 ug particulate exposure/day).[2]

Repace and Lowrey's risk estimate was severely criticized in the scientific literature.[7-12,43] ETS exposures were not evaluated or assessed in the single study relied upon by the authors for their risk estimate, yet they assumed that differences in lung cancer death rates between the Seventh Day Adventist group and the non-Seventh Day Adventist group could be ascribed solely to ETS. However, the difference in lung cancer incidence between the two groups is likely due to major lifestyle differences, including dietary habits, alcohol consumption and occupation. These possible risk factors were not adequately considered by Repace and Lowrey.

Conspicuously absent from Repace and Lowrey's current risk estimate for the workplace is any reference to, or discussion of, the 14 available epidemiologic studies on workplace exposure to ETS and lung cancer in nonsmokers.[44-57] The 14 studies report 18 risk estimates; 16 of the 18 risk estimates are not statistically significant. That is, 16 of the risk estimates are consistent with no increase in risk for nonsmokers reporting exposure to ETS in the workplace. Many of the risk ratios reported in these studies are below 1.00 -- suggesting more cases of lung cancer among nonsmokers who report no exposure at work than among those who report exposure to ETS. If the risk ratios reported in the 14 individual studies are combined and averaged in a meta-analysis like that used by the EPA in its risk assessment on ETS, the result indicates no increase

in overall risk for nonsmokers reporting exposure to ETS in the workplace.[58,59]

Specific Risk Estimates

Repace and Lowrey estimate that an "acceptable" lifetime risk for exposure to ETS-derived RSP would be .075 ug/m^3. The level of "obvious risk" for particulate exposure is established at 23 ug/m^3 by the Repace and Lowrey model. These risk estimates are based upon erroneous estimates of exposure and risk generated by the authors' previous models. For example, the estimated exposure limit for acceptable risk of .075 ug/m^3 is 3 orders of magnitude (1,000 times) lower than exposure limits established by various health agencies around the world. The level of particulate exposure from ETS designated as of "limited or no concern" by the World Health Organization is 100 ug/m^3.[60] Similarly, Canadian exposure guidelines for residential indoor air quality establish acceptable short-term exposure limits for particulate at 100 ug/m^3/hour.[61] The U.S. EPA's National Ambient Air Quality Standard for outdoor levels of (total suspended) particulate is 260 ug/m^3 for a maximum 24 hour exposure; 75 ug/m^3 annual geometric mean exposure.[62] No indoor standard for particulate exposure exists in the U.S.

The "acceptable risk" calculated by Repace and Lowrey for nicotine exposure is hundreds of times lower than the levels found in well-ventilated offices. The "acceptable risk" exposure limit for airborne nicotine of 7.5 nanograms/m^3 is below the limit of detection for most air monitoring devices. It is equivalent to the amount of nicotine found in a gram of "beefsteak" tomato.[40]

The "acceptable" or de minimis risk value calculated for cotinine corresponds to a steady-state level of 2.5 picograms of cotinine per milliliter of urine. (A picogram is one-trillionth of a gram.) This exposure limit is so low that it could be accounted for completely by the consumption of foods in an individual's ordinary diet, in the absence of all exposures to tobacco.

- The Repace/Lowrey model for cotinine predicts a median value of 6.2 nanograms/milliliter in the urine of nonsmokers in the U.S. The authors assume that this level is only achieved by exposure to ETS, but it also corresponds to the upper bound of possible contributions by dietary factors, as reported by Davis, et al. in 1991.[42]

- For an average working lifetime exposure level of 1 nanogram/milliliter of urinary cotinine, Repace and Lowrey predict a lung cancer risk of 4 per 10,000.

Again, contributions from the ordinary diet of individuals could be expected to exceed this estimated risk level. For example, an "exposure level" of 1 nanogram of cotinine could be achieved by the ingestion of four ounces of potatoes per day. Given that cotinine is both a biologically inert and non-carcinogenic substance derived from common foods, Repace and Lowrey's estimation of "excess risk" based on cotinine is reduced to absurdity.

REFERENCES

1. Repace, J., and Lowrey, A., "Indoor Air Pollution, Tobacco Smoke and Public Health," Science 208: 464-472, 1980.

2. Repace, J.L. and Lowrey, A.H., "A Quantitative Estimate of Nonsmokers' Lung Cancer Risk from Passive Smoking," Environment International 11(1): 3-22, 1985.

3. Sterling, T., "Discussion -- Tobacco Smoke, Ventilation, and Indoor Air Quality," ASHRAE Transactions 88(1): 911-912, 1982.

4. First, M., "Environmental Tobacco Smoke Measurements: Retrospect and Prospect." In: ETS -- Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels. R. Rylander, Y. Peterson, and M.-C. Snella (eds.). European Journal of Respiratory Diseases, Supplement 133, Vol. 65, 9-16, 1984.

5. Jenkins, R., and Guerin, M., "Analytical Chemical Methods for the Detection of Environmental Tobacco Smoke Constituents." In: ETS -- Environmental Tobacco Smoke: Report from a Workshop on Effects and Exposure Levels. R. Rylander, Y. Peterson, and M.-C. Snella (eds.). European Journal of Respiratory Diseases, Supplement 133, Vol. 65, 33-46, 1984.

6. First, M., "Constituents of Sidestream and Mainstream Tobacco Smoke and Markers to Quantify Exposure to Them." In: Indoor Air and Human Health. Chelsea, Michigan, Lewis Publishers, 195-203, 1985.

7. Arundel, A., Irwin, T., and Sterling, T., "Nonsmoker Lung Cancer Risks from Tobacco Smoke Exposure: An Evaluation of Repace and Lowrey's Phenomenological Model," Journal of Environmental Science and Health C4(1): 93-118, 1986.

8. Arundel, A., Sterling, T., and Weinkam, J., "Never Smoker Lung Cancer Risks from Exposure to Particulate Tobacco Smoke," Environment International 13: 409-425, 1987.

9. Lebowitz, M., "The Potential Association of Lung Cancer with Passive Smoking," Environment International 12: 3-9, 1986.

10. Johnson, C., and Letzel, H., "Letter to the Editors," Environment International 12: 21-22, 1986.

11. Burch, P., "Health Risks of Passive Smoking: Problems of Interpretation," Environment International 12: 23-28, 1986.

12. Kilpatrick, S.J., "Letter to the Editors," Environment International 12: 29-31, 1986.

13. Guerin, M., et al., The Chemistry of Environmental Tobacco Smoke: Composition and Measurement. Chelsea, Michigan, Lewis Publishers, 1992.

14. Carson, J., and Erikson, C., "Results from Survey of Environmental Tobacco Smoke in Offices in Ottawa, Ontario," Environ Technol Letters 9: 501-508, 1988.

15. Oldaker, G., et al., "Results From Surveys of Environmental Tobacco Smoke in Offices and Restaurants." In: Indoor Air Quality. H. Kasuga (ed.). Berlin, Heidelberg, Springer-Verlag, 99-104, 1990.

16. Sterling, T., and Mueller, B., "Concentrations of Nicotine, RSP, CO and CO_2 in Nonsmoking Areas of Offices Ventilated by Air Recirculated from Smoking Designated Areas," Am Ind Hyg Assoc J 49(9): 423-426, 1988.

17. Hedge, A., et al., "The Effects of Smoking Policy on Indoor Air Quality and Sick Building Syndrome in 18 Air-Conditioned Offices," IAQ 91: Healthy Buildings: 151-159, 1991.

18. Proctor, C., et al., "Measurements of Environmental Tobacco Smoke in an Air-Conditioned Office Building," Environ Technol Letters (10): 1003-1018, 1989.

19. Turner, S., et al., "The Measurement of Environmental Tobacco Smoke in 585 Office Environments," Environment International 18: 19-28, 1992.

20. Gori, G., and Mantel, N., "Mainstream and Environmental Tobacco Smoke," Regulatory Toxicology and Pharmacology 14: 88-105, 1991.

21. Adlkofer, F., "Biological Effects After Exposure to ETS," Indoor Air Quality: Symposium, Buenos Aires, National Academy of Sciences of Buenos Aires: 61-76, 1989.

22. McAughey, J., et al., "Respiratory Deposition of Environmental Tobacco Smoke." In: Indoor Air '90: The Fifth International Conference on Indoor Air Quality and Climate, Toronto, Canada. 361-366, 1990.

23. Comments of the R.J. Reynolds Tobacco Company on Appendix C to the EPA Draft Risk Assessment -- Dosimetry of Environmental Tobacco Smoke, September 1990, B-1 through C-7.

24. Holcomb, L., "Indoor Air Quality and Environmental Tobacco Smoke: Concentration and Exposure," Environment International 19: 9-40, 1993.

25. Eatough, D., et al., "The Chemical Characterization of Environmental Tobacco Smoke." In: Environmental Tobacco Smoke: Proceedings of the International Symposium at McGill University 1989. D. Ecobichon and J. Wu (eds.). Lexington, Mass., Lexington Books, 3-39, 1990.

26. Kirk, P., et al., "Environmental Tobacco Smoke in Indoor Air." In: Indoor and Ambient Air Quality. R. Perry and P. Kirk (eds.). London, Selper Ltd., 99-112, 1988.

27. Sterling, T. and Mueller, B., "ETS in Offices and When Smoking is Restricted to Designated But Not Separately Ventilated Areas." In: Indoor Air Quality. H. Kasuga (ed.). Berlin, Heidelberg, Springre-Verlag, 121-129, 1990.

28. Cummings, K., et al., "Measurement of Current Exposure to Environmental Tobacco Smoke," Archives of Environmental Health 45(2): 74-79, 1990.

29. Curvall, M., et al., "Simulation and Evaluation of Nicotine Intake During Passive Smoking: Cotinine Measurements in Body Fluids of Nonsmokers Given Intravenous Infusions of Nicotine," Clin Pharmacol Ther 47(1): 42-49, 1990.

30. Idle, J., "Commentary: Titrating Exposure to Tobacco Smoke Using Cotinine -- A Minefield of Misunderstanding," Journal of Clinical Epidemiology 43(4): 313-317, 1990.

31. Haley, N., et al., "Elimination of Cotinine from Body Fluids: Disposition in Smokers and Nonsmokers," AJPH 79(8): 1046-1048, 1989.

32. Johnson, L., et al., "Passive Smoking Under Controlled Conditions," Int Arch Occup Environ Health 56: 99-110, 1985.

33. Letzel, H., et al., "Measuring Problems in Estimating the Exposure to Passive Smoking Using the Excretion of Cotinine," Toxicology Letters 35(1): 35-44, 1987.

34. Proctor, C., "Multi-Analyte Approach to the Measurement of Environmental Tobacco Smoke," Indoor Air Quality and Ventilation 427-436, 1990.

35. Schwartz, S., et al., "Mathematical Modelling of Nicotine and Cotinine as Biological Markers of Environmental Tobacco Smoke Exposure," Toxicology Letters 35(1): 53-58, 1987.

36. Coultas, D., et al., "Questionnaire Assessment of Lifetime and Recent Exposure Tobacco Smoke," American Journal of Epidemiology 130(2): 338-347, 1989.

37. Coultas, D., et al., "Variability of Measures of Exposure to Environmental Tobacco Smoke in the Home," American Review of Respiratory Disease 142: 602-606, 1990.

38. Coultas, D., et al., "A Personal Monitoring Study to Assess Workplace Exposure to Environmental Tobacco Smoke," American Journal of Public Health 80(8): 988-990, 1990.

39. Domino, E., "The Nicotine Content of Common Vegetables," NEJM 329(6): 437, 1993.

40. Castro, A., Monji, N., "Dietary Nicotine and its Significance in Studies on Tobacco Smoking," Biochem Arch 2:91-7, 1986.

41. Sheen, S., Detection of Nicotine in Foods and Plant Materials. J Food Sci 53:1572-3, 1988.

42. Davis, R., et al., Dietary Nicotine: A Source of Urinary Cotinine. J Food Chem Toxicol (29): 821-7, 1991.

43. Gross, A., "Risk Assessments Relating to Environmental Tobacco Smoke." In: Environmental Tobacco Smoke: Proceedings of the International Symposium at McGill University. Lexington Mass., Lexington, Books, 293-302, 1990.

44. Kabat, G., and Wynder, E., "Lung Cancer in Nonsmokers," Cancer 53: 1214-1221, 1984.

45. Garfinkel, L., et al., "Involuntary Smoking and Lung Cancer: A Case-Control Study," Journal of the National Cancer Institute 75(3): 463-469, 1985.

46. Lee, P., et al., "Relationship of Passive Smoking to Risk of Lung Cancer and Other Smoking-Associated Diseases," British Journal of Cancer 54: 97-105, 1986.

47. Koo, L.C., et al., "Is Passive Smoking an Added Risk Factor for Lung Cancer in Chinese Women?" J Exp Clin Cancer Res 3(3): 277-283, 1984.

48. Shimizu, H., et al., "A Case-Control Study of Lung Cancer in Nonsmoking Women," Tohoku Journal of Experimental Medicine 154: 389-397, 1988.

49. Butler, T., "The Relationship of Passive Smoking to Various Health Outcomes Among Seventh Day Adventists in California," dissertation submitted to University of California, Los Angeles, 1988.

50. Janerich, D., et al., "Lung Cancer and Exposure to Tobacco Smoke in the Household," The New England Journal of Medicine 323: 632-636, 1990.

51. Kabat, G., "Epidemiologic Studies of the Relationship Between Passive Smoking and Lung Cancer," Toxicology Forum, 1990 Annual Winter Meeting (transcript): 187-199, 1990.

52. Kalandidi, A., et al., "Passive Smoking and Diet in the Etiology of Lung Cancer Among Non-Smokers," Cancer Causes and Control 1: 15-21, 1990.

53. Wu-Williams, A., et al., "Lung Cancer Among Women in North-East China," British Journal of Cancer 62: 982-987, 1990.

54. Wu, A., et al., "Smoking and Other Risk Factors for Lung Cancer in Women," JNCI 74(4): 747-751, 1985.

55. Fontham, E., et al., "Environmental Tobacco Smoke and Lung Cancer in Nonsmoking Women: A Multicenter Study," JAMA 271: 1752-1759, 1994.

56. Stockwell, H., et al., "Environmental Tobacco Smoke and Lung Cancer Risk in Nonsmoking Women," JNCI 84: 1417-1422, 1992.

57. Brownson, R., et al., "Passive Smoking and Lung Cancer in Nonsmoking Women," Am J Publ Health 82: 1525-1530, 1992.

58. Lee, P., Environmental Tobacco Smoke and Mortality. Basel, Karger, 1992.

59. LeVois, M., and Layard, M., "Inconsistency Between Workplace and Spousal Studies of Environmental Tobacco Smoke and Lung Cancer," Reg Tox and Pharm 19: 309-316, 1994.

60. World Health Organization, Report on a WHO meeting, August 21-24, 1984, Indoor Air Quality Research, EURO Reports and Studies 103, Regional Office for Europe, Copenhagen, Denmark.

61. Canadian Department of National Health and Welfare, Exposure Guidelines for Residential Indoor Air Quality. Ottawa, April 1987.

62. U.S. Environmental Protection Agency, Code of Federal Regulations, Title 40, Part 50 (Current National Ambient Air Quality Standards).

APPENDIX C

PHARMACOKINETIC MODELING

PHARMACOKINETIC MODELING

COTININE IS NOT A RELIABLE QUANTITATIVE MARKER OF EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE IN NONSMOKERS

In its Proposed Rule on IAQ/ETS, OSHA suggests that cotinine, a substance converted from nicotine in the body, can be used as a biological marker to measure nonsmoker exposure to ETS. OSHA assumes, however, a direct correlation between exposure to nicotine in the ambient air and the existence of cotinine in body fluids. However, research indicates that such a correlation does not exist, for a number of reasons.[1-11] For example, researchers have reported that individuals metabolize nicotine in different ways at different times and that elimination rates for cotinine vary among individuals. In addition, recent research indicates that diet may contribute to levels of nicotine and cotinine found in the body, thereby interfering with ambient air exposure levels.[12] Scientists have also noted that different laboratory methods of analysis may influence final recorded levels of cotinine.[13] And finally, because cotinine is a metabolite of a gas-phase constituent of ETS, nicotine, cotinine levels do not represent exposures to other constituents of ETS.

The published literature on possible nicotine-cotinine correlations indicates enormous variability between the two proposed ETS markers. For example, Cummings, et al. (1990) wrote:

"Within a given exposure level there was considerable variability in cotinine values. Cotinine was chosen as a biological marker of ETS exposure because it is specific to tobacco smoke. However, cotinine levels in body fluids may not only reflect environmental exposure to tobacco smoke, but also factors that influence uptake and metabolism of nicotine."[5] The authors concluded:

> The relatively modest correlation between reported ETS exposure and urinary cotinine indicated that other factors such as differing metabolic rates and body size may have a confounding effect on the relationship between cotinine levels and questionnaire measures of ETS exposure. In view of this finding, we would recommend against using cotinine levels as a strictly quantitative indicator of ETS.

Similarly, research in 1985 by Johnson and colleagues indicated that: "[D]espite an identical exposure rate, considerable interindividual variability of subsequent nicotine and cotinine levels in saliva, plasma and 24-h urine were observed."[9]

Haley and coauthors reported in 1989 that the results of their study supported the concept that "cotinine elimination can be more rapid in smokers than in nonsmokers who are exposed to ETS."[7] They also noted that "differences in the mode of uptake and absorption of nicotine and possible differences in nicotine metabolism may play roles in the clearance rate differences between smokers and nonsmokers."

In 1990, Japanese researchers examined the relationship between nicotine and cotinine levels in plasma and urine.[6] The results of their study indicated no consistent correlation among the four exposure markers for ETS, i.e., no consistent association between nicotine levels in plasma and urine with cotinine levels in plasma and urine.

In a commentary published in 1990, Jeffrey Idle of the Department of Pharmacological Sciences at the University of Newcastle in the United Kingdom wrote:[4]

> My own dissatisfaction with indiscriminate use of cotinine as a dosimeter of tobacco smoke arises from a trade-off of knowledge for convenience . . . [T]he extent of intersubject variability in human disposition of nicotine and its metabolites is both nebulous and poorly understood. The complex of dynamic interactions which leads to a certain salivary or urinary concentration of cotinine at one point in time following exposure to a defined among of airborne nicotine needs to be dissected . . . [S]ingle point cotinine concentrations can give no more than a clue to a past exposure to pyridine alkaloids of unknown amount, at an unspecified time, by an unknown route of entry and from unknown origins.

Curvall and co-workers, in a report published in 1990, wrote:[1]

> The estimation of nicotine intake from cotinine concentrations in body fluids is valid only if the metabolism of nicotine and the subsequent elimination of cotinine are independent of the dose. The pharmacokinetics of nicotine and cotinine have been evaluated in smokers and nonsmokers at concentrations usually achieved by smokers, and little is known about the kinetics of these compounds at concentrations found in nonsmokers exposed to environmental tobacco smoke nicotine . . . the suitability of cotinine as a marker of environmental tobacco smoke nicotine exposure has only been evaluated in field studies; no data are available on the relationship between low dose nicotine intake and cotinine concentrations in nonsmokers. [emphasis added]

Similarly, in 1991, Proctor and associates reported on correlations among salivary cotinine levels, salivary nicotine levels, observed number of cigarettes smoked, and ambient exposure to ETS.[14] Correlations, on balance, were so poor that the researchers remarked that "this raises doubt about the validity of salivary cotinine information at low levels and suggests that studies that have suggested large portions of the population are being exposed to ETS may be misleading (Repace and Lowrey 1985; Wells 1988)."

Another report by Proctor (1990) reached a similar conclusion.[15] He wrote:

> The data shows [sic] little correlation between number of cigarettes smoked during the sampling period and salivary cotinine at t_2 or

with a change in salivary cotinine t_2-t_1. Furthermore, there is little correlation between personal exposures to nicotine and salivary cotinine at t_2 or t_2-t_1.

Other reviewers, Gori and Mantel, observed the following:[16]

> Hopes have been placed on nicotine and its metabolite cotinine as possible markers of ETS intake and actual internal dose . . . Unfortunately ETS-nicotine resides mostly in the gas phase and decays at rates quite different from other ETS components, to which it will have ratios that are variable in time and largely unpredictable . . . Plasma cotinine levels suffer from similar and other shortcomings, although they have been shown to correlated with self-reported exposure to ETS. Reports also suggest that physiologic clearance of nicotine and cotinine at low plasma levels may proceed at much slower rates, likely because of slower release from preferential body compartments. Until these low-level kinetics are better understood, low plasma levels of nicotine and cotinine are likely to lead to substantial overestimations of intake doses. As such, nicotine and cotinine may provide a dichotomous index of contemporary exposure, but they remain inadequate as quantitative estimators of exposure, actual ETS dose, or their variation over an individual's life.

Another group of authors suggests, "at best, cotinine is a semi-quantitative marker of nicotine exposure, and even then only if sampling protocols take into account the relationship between the time of exposure and the time of sampling."[3] [emphasis added]

In 1990, Lewis, et al., reported that "the variability in nicotine transport and metabolism complicates the use of urine nicotine and cotinine in assessing ETS exposure."[17]

In summary, cotinine has been used effectively for smoking classification purposes because concentrations of cotinine reported in smokers are substantially higher than those reported for nonsmokers. The claim that cotinine is also a reliable measure of ETS exposure, however, presents an issue that has been challenged in the scientific literature. A thorough and complete review of the literature suggests that, at best, cotinine may be used as a qualitative marker of ambient nicotine exposures. Consequently, attributable risk and exposure models based upon cotinine are seriously compromised.

NICOTINE IS NOT SPECIFIC TO TOBACCO SMOKE EXPOSURE

One of the major problems with the use of cotinine as a measure of ETS exposure is that it assumes that nicotine is specific only to tobacco smoke exposure, and that exposures to nicotine in the air can be directly related to cotinine levels in the body. Neither assumption is correct.[1-16, 18-21] It has recently been discovered that common foods -- potatoes, tomatoes, eggplant and other fruits and vegetables -- naturally contain small amounts of nicotine, which is subsequently converted by the body to

cotinine.[19-21] Nonsmokers who are not exposed to ambient nicotine from ETS nevertheless will have detectable body fluid levels of cotinine due to dietary ingestion of foods containing nicotine.[19]

Therefore, as one author has suggested:[4]

> Cotinine is variously described as 'a particularly specific and sensitive marker of exposure to tobacco smoke', 'a useful and reliable indicator of nicotine intake' and 'a reliable indicator of tobacco smoke exposure'. These statements deserve further comment in the light of the recent finding of nicotine both in Solanaceae plants which are consumed as vegetables in our diet and in instant tea preparations. Whilst nicotine, with the exception of carbon monoxide, is the most abundant single chemical in tobacco smoke, with an estimated yield of 1.0-2.3 mg per cigarette, with a mean nicotine intake per cigarette calculated as 0.75-1.25 mg per cigarette, it can no longer be considered as tobacco-specific.

CONCENTRATIONS OF NICOTINE AND ITS METABOLITE, COTININE, IN THE BODY ARE NOT VALID MARKERS OF ANY SPECIFIC POTENTIAL HEALTH EFFECTS IN NONSMOKERS EXPOSED TO ENVIRONMENTAL TOBACCO SMOKE

OSHA's claim suffers from at least two major problems. First, because nicotine is present largely in the gas phase of ETS, it cannot be relied upon to estimate exposure to other ETS constituents present in the particulate phase. Second, nicotine and cotinine in body fluids are not markers for specific potential

health effects in nonsmokers or for reported mutagenicity in the urine of nonsmokers exposed to ETS. Kopczynski reported in 1989 that "further investigation of smoking and environmental variables is needed to validate the use of cotinine as a marker compound for environmental tobacco smoke particulate matter."[22] As one author writes:[3]

> The first issue is whether the nicotine exposure of an individual exposed to ETS follows the exposure of the individual to other components of ETS. Unless it can be demonstrated that changes in the behavior of nicotine in air with time parallel those of other components, especially those that may be associated with the toxicity of ETS, then biomarker studies of nicotine or cotinine will reflect only nicotine exposure, and cannot be used as a basis for extrapolation to ETS per se.

Another author suggests:[23]

> [C]otinine in plasma, urine and saliva is presently the most reliable biomarker for ETS exposure as long as comparisons are limited to subjects with different degrees of ETS exposure. Extrapolation from the uptake of nicotine to that of other tobacco smoke constituents is of doubtful validity due to a more rapid removal of nicotine than other components from ETS in indoor environments.

The contention that nicotine and cotinine levels in body fluids are not markers of the potential mutagenicity of ETS is supported by several studies which have reported elevated levels of

cotinine in the body fluids of nonsmokers exposed to ETS compared with nonsmokers not exposed to ETS but have reported no differences in various measures of mutagenicity in the two groups of nonsmokers.[23-30] One group of researchers reported an inverse relationship between the levels of cotinine in the urine and the level of mutagens in the urine in nonsmokers.[31] They reported:

> Urinary mutagenicity levels (mean ± SE) were 509 ± 186 revertants per millimole in the 11 nonsmokers exposed to passive smoking with no cotinine or nicotine in the urine and 182 ± 182 revertants per millimole in the 4 nonsmokers with measurable levels of these markers . . .

Other authors emphasize that nicotine and cotinine "are not responsible for the mutagenicity of smokers' urine."[32] One author summarized the topic as follows:[33]

> Urinary cotinine/creatinine ratio is a useful marker for estimating personal ETS exposure levels. But this marker does not reveal health effects caused by involuntary smoking because it is too speculative to conclude that high level urinary or serum cotinine levels directly indicate the possibility of disorders in the human body.

REFERENCES

1. Curvall, M., et al., "Simulation and Evaluation of Nicotine Intake During Passive Smoking: Cotinine Measurements in Body Fluids of Nonsmokers Given Intravenous Infusions of Nicotine," Clin Pharmacol Ther 47(1): 42-49, 1990.

2. Biber, A., et al., "Determination of Nicotine and Cotinine in Human Serum and Urine: An Interlaboratory Study," Toxicology Letters 35(1): 45-52, 1987.

3. Balter, N.J., et al., "Application of Physiological Pharmacokinetic Modeling to the Design of Human Exposure Studies with Environmental Tobacco Smoke." In: Indoor and Ambient Air Quality. Kirk, et al., (eds.). Selper Limited, 1988.

4. Idle, J., "Commentary: Titrating Exposure to Tobacco Smoke Using Cotinine -- A Minefield of Misunderstanding," Journal of Clinical Epidemiology 43(4): 313-317, 1990.

5. Cummings, K., et al., "Measurement of Current Exposure to Environmental Tobacco Smoke," Archives of Environ Health 45(2): 74-79, 1990.

6. Itani, S., et al., "A Comparison of Plasma and Urinary Nicotine and Cotinine Levels in Smokers and Nonsmokers: Nicotine Excretion Pathways are Possibly Differential According to the Dosage of Tobacco Smoke Uptake." In: Indoor Air Quality. H. Kasuga (ed.). Springer-Verlag, Berlin, Heidelberg, 202-212, 1990.

7. Haley, N., et al., "Elimination of Cotinine from Body Fluids: Disposition in Smokers and Nonsmokers," AJPH 79(8): 1046-1048, 1989.

8. Lee, P., "Lung Cancer and Passive Smoking," Br J Cancer 63: 161-162, 1991.

9. Johnson, L., et al., "Passive Smoking Under Controlled Conditions," Int Arch Occup Environ Health 56: 99-110, 1985.

10. Letzel, H., et al., "Measuring Problems in Estimating the Exposure to Passive Smoking Using the Excretion of Cotinine," Toxicology Letters 35(1): 35-44, 1987.

11. Schwartz, S., et al., "Mathematical Modelling of Nicotine and Cotinine as Biological Markers of Environmental Tobacco Smoke Exposure," Toxicology Letters 35(1): 53-58, 1987.

12. Castro, A., and Monji, N., "Dietary Nicotine and Its Significance in Studies on Tobacco Smoking," Bio Arch 2(2): 9197, 1986.

13. Adlkofer, F., et al., "Passive Smoking," New England Journal of Medicine 312(11): 719-720, 1984.

14. Proctor, C., et al., "A Comparison of Methods of Assessing Exposure to Environmental Tobacco Smoke in Non-Smoking British Women," Environ International 17: 287-297, 1991.

15. Proctor, C., "Multi-Analyte Approach to the Measurement of Environmental Tobacco Smoke," Indoor Air Quality and Ventilation: London, Selper Ltd., 427-436, 1990.

16. Gori, G. and Mantel, N., "Mainstream and Environmental Tobacco Smoke," Reg Tox and Pharm 14: 88-105, 1991.

17. Lewis, E.A., et al., "Use of Urine Nicotine and Cotinine Measurements to Determine Exposure of Nonsmokers to Sidestream Tobacco Smoke," Proc Int Conf Indoor Air Qual Clim 0(5): 151-156, 1990.

18. Reasor, M. and Will, J., "Assessing Exposure to Environmental Tobacco Smoke: Is It Valid to Extrapolate from Active Smoke?," Journal of Smoking Related Diseases 2(1): 111-127, 1991.

19. Davis, R., "Dietary Nicotine: A Source of Urinary Cotinine," Fd Chem Toxic 29(12): 821-827, 1991.

20. Domino, E., et al., "The Nicotine Content of Common Vegetables," NEJM 329(6): 437, 1993.

21. Domino, E., et al., "Relevance of Nicotine Content of Common Vegetables to the Identification of Passive Tobacco Smokers," Med Sci Res (21): 571-572, 1993.

22. Kopczynski, S.L., "Multidimensional Gas Chromatographic Determination of Cotinine as a Marker Compound for Particulate-Phase Environmental Tobacco Smoke," Journal of Chromatography 463: 253-260, 1989.

23. Scherer, G, et al., "Uptake of Tobacco Smoke Constituents on Exposure to Environmental Tobacco Smoke," Clin Investig 70: 352-367, 1992.

24. Gorgels, W.J.M.J., et al., "Passive Smoking and Sister-Chromatid Exchanges in Lymphocytes," Mutation Research 279: 233-238, 1992.

25. Scherer, G., et al., "Biomonitoring of Exposure to Potentially Genotoxic Substances from Environmental Tobacco Smoke," Environment International 15: 49-56, 1989.

26. Scherer, G, et al., "Urinary Mutagenicity, Hydroxyphenanthrene, and Thioether Excretion After Exposure to Environmental Tobacco Smoke," Int Arch Occup Environ Health Suppl 0(0): 138-146, 1990.

27. Scherer, G., et al., "Quantitative and Qualitative Differences in Tobacco Smoke Uptake Between Active and Passive Smoking," Indoor and Ambient Air Quality, R. Perry and P. Kirk (eds.). London, Selper Ltd., 189-194, 1988.

28. Scherer, G., et al., "Urinary Mutagenicity After Controlled Exposure to Environmental Tobacco Smoke (ETS)," Toxicology Letters 35: 135-140, 1987.

29. Sorsa, M., et al., "Cytogenic Effects of Tobacco Smoke Exposure Among Involuntary Smokers," Mutation Research 222(2): 111-116, 1989.

30. Husgafvel-Pursiainen, K., et al., "Passive Smoking at Work: Biochemical and Biological Measures of Exposure to Environmental Tobacco Smoke," Int Arch Occup Environ Health 59: 337-345, 1987.

31. Bartsch, H., et al., "Carcinogen Hemoglobin Adducts, Urinary Mutagenicity, and Metabolic Phenotype in Active and Passive Cigarette Smokers," Journal of the National Cancer Institute 82: 1826-1831, 1990.

32. Rahn, C.A., et al., "Correlations Between Urinary Nicotine or Cotinine and Urinary Mutagenicity in Smokers on Controlled Diets," Environmental and Molecular Mutagenesis 17: 244-252, 1991.

33. Matsuki, H., et al., "Biological Effects Associated with Exposure to Environmental Tobacco Smoke: Involuntary Smoking and Urinary Cotinine," Int Arch Occup Environ Health Suppl 0(0): 194-201, 1990.